

---

**Design, Development and Initiation  
of the  
Liverpool Respiratory Birth  
Cohort Study**

*Thesis submitted in accordance with the requirements of  
the University of Liverpool for the degree of Master in  
Philosophy*

*by*

**Rosanna E Pickles**

---

July 2013

---

# I. ACKNOWLEDGEMENTS

There are numerous individuals that I would like to thank for their support and guidance throughout my time undertaking this MPhil. I would like to begin by sincerely thanking my primary supervisor Dr Calum Semple for his continued invaluable guidance and support with this project for which I am extremely grateful. I am also extremely grateful to Professor Ben Shaw for his expertise and guidance throughout the development and initiation of this project. I would also like to thank Dr Kevin Southern and Dr Paul McNamara for their guidance and advice with this project.

A special thanks goes to my fellow co-worker and MPhil student Bethan Griffiths for her truly invaluable help, support and work with this study. She has not only inspired and motivated me but also provided great deal of entertainment over the past academic year! I truly wish her all the best with the continuation of this project and her future career.

I would like to thank Miss Louise Hardman and Gillian Vernon from the Liverpool Women's Hospital Primary Care Trust, who provided invaluable advice during the ethical application process in addition to their administrative support. I would like to thank Gemma Boydell from the Alder Hey Children's Hospital IT Department and to Moira Saphier at the Institute of Child Health for their invaluable support with the administration of the study. I also would like to extend my gratitude to mothers who have expressed an interest in this study and particularly those who have consented and completed the initial questionnaire, without which the study has no opportunity for success.

I would like to thank my fellow MPhil students (both past and current years), and staff at the Institute of Child Health for their encouragement and friendship. I would also like to thank my close friends for their support and encouragement throughout this MPhil who have somehow helped me maintain my sanity throughout the entire process!

Finally I would like to thank my remarkable and loving parents. Without whom I could not have considered or undoubtedly completed this project. Their love, guidance and support provided me with this valuable opportunity and gave me the strength to complete it. I dedicate this thesis to my sister.

## II. ABBREVIATIONS

AFC	Adobe® FormsCentral
AH	Alder Hey Children's Hospital
ALSPAC	Avon Longitudinal Study of Parents and Children
ATSq	American Thoracic Society Standardized Respiratory Questionnaire
BCS70	1970 British Cohort Study
CCG	Clinical Commission Group
CF	Cystic Fibrosis
COPD	Chronic Obstructive Pulmonary Disease
DDA	Doctor Diagnosed Asthma
DDOS	Distributed Denial of Service
EC	Electronic Communications
ELSPAC	European Longitudinal Study of Pregnancy and Childhood
ESRC	Economic and Social Research Council
GA2LENq	Global Allergy and Asthma European Network Questionnaire
GP	General Practitioner
HRQL	Health Related Quality of Life
hRSV	Human Respiratory Syncytial Virus
HTML	Hypertext Markup Language
ID	Identification
IgE	Immunoglobulin E
IHD	Ischeamic Heart Disease
IMD	Indices of Multiple Deprivations
IP	Internet protocol
IRAS	Integrated Research Approval System
ISAAC	International Study of Asthma and Allergies in Childhood
ITG-CASF	Integrated Therapeutics Group Child Asthma Short Form
LRBCS	Liverpool Respiratory Birth Cohort Study
LRSQ	Liverpool Respiratory Symptom Questionnaire
LRTI	Lower Respiratory Tract Infection
LSOA	Lower Layer Super Output Area
LWH	Liverpool Women's Hospital

MAAS	The Manchester Asthma and Allergy Study
MCS	Millennium Cohort Study
MDI	Multiple Deprivation Index
MRC	Medical Research Council
MRCq	Medical Research Council Respiratory Questionnaire
MRHS	Merseyside Respiratory Health Surveys
NCDS	National Child Development Study
NETSCC	NIHR Evaluation, Trials and Studies Coordinating Centre
NHS	National Health Service
NICE	National Institute of Clinical Excellence
NRES	National Research Ethics Service
NSHD	National Survey of Health & Development
PCT	Primary Care Trust
PDF	Portable Document Formula
PDS	Patient Demographic Service
PPI	Patient and Public Involvement
QoL	Quality of Life
QR	Quick Response
REC	Research Ethics Committee
RPBDA	Respiratory physicians based diagnosis of asthma
SPSS	Statistical Package for the Social Sciences
SQL	Structured Query Language
SQRQ	St George Respiratory Questionnaire
SS	SelectSurvey.NET
SSL	Secure Sockets Layer
TI	Townsend Index
TRACK	Test for Respiratory and Asthma Control in Kids
URL	Uniform Resource Locator
WMA	World Medical Association
WURSS44	Wisconsin Upper Respiratory Symptom Survey



### III. ABSTRACT

**Objective:** To design, develop and initiate the Liverpool Respiratory Birth Cohort Study (LRBCS). This longitudinal birth cohort study aims to describe the respiratory symptoms of preschool children using the Liverpool Respiratory Symptom Questionnaire (LRSQ) from birth until the age of 5 years in Liverpool, by bi-annual assessment.

**Introduction:** Respiratory symptoms in preschool children are difficult to assess using objective measures; indirect measures such as parental completed respiratory symptom questionnaires offer a valuable alternative. The LRSQ is one of few respiratory questionnaires validated for preschool populations. Using the LRSQ, this unique birth cohort study not only maps respiratory symptoms of Liverpool preschool children, but also explores the impact of these symptoms upon the child and their parents.

**Method:** The LRBCS protocol was developed in collaboration with experienced paediatricians. Ethical approval was obtained by proportionate review in May 2012. As questionnaire deployment would be primarily conducted online, web-based survey software and an email-scheduling system were imperative for development and deployment of the questionnaire. Viable options for survey software were ascertained by feasibility testing at the LWH while providing an opportunity to tailor the design, appearance and accessibility of the questionnaire to appeal to the target population, while maintaining usability. MailChimp® was identified as the most efficient automated email scheduling service. Recruitment was piloted to determine the most effective strategy.

**Analysis:** Recruitment has been successful to date, with Mothers of 1330 infants expressing interest (53% of eligible births) by 31<sup>st</sup> May 2013. Furthermore 80 Mothers (27% of those expressing interest) consented and returned data regarding their infant's respiratory symptoms four months after birth. Preliminary analysis has shown that the group of Mothers expressing interest are representative of Liverpool's new mothers and the local population in terms of demographics. Demographic, exposure and LRSQ data was collected online by Adobe Forms Central and by post questionnaires, and then collated using SPSS V19 for analysis.

**Conclusion:** The LRBCS has been initiated successfully. It is an ongoing birth cohort study that will proceed for a further 6 years minimum, producing a large variety of invaluable data detailing the respiratory health and characteristics of the preschool Liverpool population. Future analysis will enable the exploration of demographic and exposure factors affecting the respiratory health of the Liverpool preschool population.

## IV. TABLE OF CONTENTS

<b>I</b>	<b>Acknowledgements</b>	<b>2</b>
<b>II</b>	<b>Abbreviations</b>	<b>3</b>
<b>III</b>	<b>Abstract</b>	<b>5</b>
<b>IV</b>	<b>Table of Contents</b>	<b>6</b>
<b>V</b>	<b>List of Tables</b>	<b>9</b>
<b>VI</b>	<b>List of Figures</b>	<b>10</b>
<b>1</b>	<b>Introduction</b>	<b>11</b>
1.1	<i>Respiratory Symptoms in Preschool Children</i>	11
1.1.1	The Natural History of the Respiratory Symptoms in Preschool Children	11
1.2	<i>Current Respiratory Symptom Questionnaires</i>	14
1.2.1	Adult Questionnaires	15
1.2.2	Paediatric Questionnaires	18
1.2.3	Studying Preschool Respiratory Symptoms	20
1.3	<i>The LRSQ and Supporting Evidence</i>	22
1.4	<i>Birth Cohort Studies</i>	28
1.4.1	What are they?	28
1.4.2	National British Birth Cohort Studies	29
1.4.3	Regional British Birth Cohort Studies	37
1.4.4	National and International Birth Cohort Studies	41
1.5	<i>Conclusion</i>	44
2.1	<i>Justification of the LRBCS</i>	45
2.1.1	Using the LRSQ	45
2.1.2	Respiratory Disease in the United Kingdom	46
2.1.3	Respiratory Disease in Liverpool	47
2.1.4	Deprivation in Liverpool	50
2.1.5	Recruitment at the Liverpool Women's Hospital	52
2.2	<i>Method Development</i>	54
2.2.1	Demographic and Exposure Data	54
2.2.2	Consent, Recruitment and Retention Strategies	55
2.2.3	Questionnaire Deployment	55
2.3	<i>Revisions to Protocol</i>	56
2.4	<i>The Protocol</i>	58
	Figure 2.4 Exposure variables	64
	Figure 2.3 Demographics	64
2.5	<i>Conclusion</i>	76
<b>3</b>	<b>Application to Ethics</b>	<b>77</b>
3.1	<i>Introduction</i>	77
3.1.1	Getting Started with IRAS	77
3.1.2	The Importance of Ethical Approval	77
3.2	<i>Factors for consideration</i>	79
3.3	<i>Study Documentation</i>	81
3.3.1	Participant Information Sheet (PIS)	81
3.3.2	Participant Recruitment Postcard	81
3.3.3	Consent Form	82

3.3.4	Demographic and Exposure Questionnaire	82
3.3.5	Power point presentation mock up of proposed online documentation	82
3.3.6	The LRSQ	83
3.4	Sponsorship	83
3.5	Amendments	84
3.5.1	First Minor Amendments	84
3.5.2	Second Minor Amendments	85
3.6	Conclusion	86
<b>4</b>	<b>Questionnaire Development</b>	<b>87</b>
4.1	Introduction	87
4.1.1	The Truth About Web-Based Questionnaires	87
4.1.2	Web-based Questionnaires and the LRBCS	96
4.2	Justification of Software	97
4.2.1	Survey Software Options	97
4.2.2	SelectSurvey.Net vs Adobe Forms Central	98
4.3	Mailing software	100
4.3.1	MailChimp®	101
4.4	Developing the Online Questionnaire	104
4.4.1	Design Considerations	104
4.4.2	Software advantages and limitations	106
4.5	Conclusion	109
<b>5</b>	<b>Feasibility Testing</b>	<b>110</b>
5.1	Introduction	110
5.1.1	What are Feasibility Studies?	110
5.1.2	What is the Importance of Feasibility testing?	112
5.1.3	How does this link in with the LRBCS?	112
5.2	LRBCS: Patient and Public Involvement	113
5.2.1	Aim	113
5.2.2	Introduction	113
5.2.3	Method	115
5.2.4	Results	119
5.2.5	Discussion	122
5.2.6	Conclusion	124
5.2.7	Limitations	124
5.3	Feasibility: Adobe FormsCentral vs SelectSurvey.NET	125
5.3.1	Aim	125
	To assess the feasibility, usability and readability of the online LRSQ, using both Adobe® Forms Central (AFC) and SelectSurvey.NET software (SS).	125
5.3.2	Introduction	125
5.3.3	Method	125
5.3.4	Results	127
5.4	Discussion	130
5.5	Conclusion	133
5.6	Limitations	134
5.7	LRBCS: Estimated Cost	135
5.8	Conclusion	138
<b>6</b>	<b>Recruitment Pilot</b>	<b>139</b>
6.1	Background	139
6.1.1	Preparation	140
6.1.2	Administration	140

6.1.3	Plan	141
6.2	<i>Recruitment Pilot</i>	141
6.2.1	Method	141
6.2.2	Results	142
6.2.3	Conclusion	149
6.3	<i>Final Recruitment Strategy</i>	149
6.4	<i>Recruitment Results To Date</i>	150
6.5	Conclusion	151
<b>7</b>	<b>Discussion &amp; Conclusion</b>	<b>152</b>
7.1	<i>Discussion</i>	152
7.2	<i>Strengths of the Study</i>	158
7.3	<i>Study Limitations</i>	160
7.4	<i>Potential Bias and Confounding Factors in Birth Cohort Studies</i>	162
7.5	<i>Future Work and Data Analysis</i>	164
7.5.1	Future Work	164
7.5.2	Data Analysis	167
7.6	Conclusion	169
<b>8</b>	<b>References</b>	<b>170</b>
	<b>Appendix</b>	<b>188</b>
	<i>Appendix 1 –Literature Review Tables</i>	189
	<i>Appendix 2 – IRAS Application Documentation</i>	193
	<i>Appendix 3 – Summary of Articles Evaluating Online Questionnaires</i>	207
	<i>Appendix 4 – Feasibility Studies Documentation</i>	210
	<i>Appendix 5 – LRBCS Initial Questionnaire</i>	219
	<i>Appendix 6 – Statistical Results</i>	235
	<i>Appendix 7 – Mailing Schedule</i>	236

## V. LIST OF TABLES

Table 1.1	Summary of the domains of the Liverpool Respiratory Symptom Questionnaire (LRSQ)
Table 2.1	Risk factors for respiratory symptoms in paediatrics
Table 2.2	Summary of Protocol Revisions
Table 4.1	Summary of pros and cons of web-based questionnaires
Table 4.2	Factors that improve response rates in web surveys
Table 4.3	Survey Building Software Trained
Table 4.4	Comparison of Survey Software (courtesy of B. Griffith)
Table 5.1	Factors that Optimise Questionnaire Design
Table 5.2	Summary of Prototype Domains and Questions
Table 5.3	LRBCS Start-up Cost
Table 5.4	LRBCS Total Cost
Table 6.1	Pilot Recruitment Plan
Table 6.2	Summary of Pilot Recruitment Results
Table 6.3	Proportion of Infants per ethic group in comparison to the Liverpool baseline population

## VI. LIST OF FIGURES

Figure 2.1	Deprivation in Liverpool by Semple et al
Figure 2.2	Map showing location of LWH within the Liverpool Postcodes
Figure 2.3	LRBCS Study Method
Figure 2.4	Demographics
Figure 2.5	Exposure Variables
Figure 2.6	Gantt Chart Showing Protocol Development and NRES Application Timescale
Figure 4.1	Preview of an Email Drafted by MailChimp®
Figure 4.2	Example of Matrix Style Question
Figure 4.3	Example of Dropdown Style Questions
Figure 4.4	Example of the Finalised, SelectSurvey.NET-Version
Figure 5.1	NETSCC Summary of Important Parameters
Figure 5.2	Page Density Preferences
Figure 5.3	Background Design Preferences
Figure 5.4	Font Size Preference
Figure 5.5	Theme Preference
Figure 5.6	Summary of additional feedback from Mothers
Figure 5.7	First Impression Preference
Figure 5.8	Comparison of Survey Software Usability
Figure 5.9	LRBCS Question Style Preference
Figure 5.10	QR Sign-Up Code for the LRBCS
Figure 5.11	Overall Software Preference
Figure 5.12	Additional Feedback from Mothers
Figure 5.13	Revisions to Demographic and Exposure Questions
Figure 5.14	Additional Revisions Following Feasibility Study
Figure 6.1	Description of the two-stage Recruitment Process
Figure 6.2	Outcome of Infants born at the Liverpool Woman's Hospital
Figure 6.3	Proportion of Infants per Liverpool Postcode
Figure 6.4	Geographical Representation of Expressed Interest and Maternity Services
Figure 6.5	Proportion of Infants by IMD Deprivation Quintile
Figure 6.6	Cumulative Total for Expressed Interest and Consent
Figure 7.1	Gantt Chart showing the development of the LRBCS
Figure 7.2	Measures of longitudinal data analysis

# 1 Introduction

## 1.1 Respiratory Symptoms in Preschool Children

### 1.1.1 The Natural History of the Respiratory Symptoms in Preschool Children

The most common respiratory symptoms children under the age of five experience are wheeze and cough, other symptoms include shortness of breath<sup>3-5</sup>. Major studies have reported the prevalence of wheeze in preschool children as being between 25% and 38%<sup>3, 5-7</sup>. Preschool children reportedly suffer from disproportionately more wheeze than older children aged 5–16 years<sup>8</sup>. Previous studies describe wheeze as a transient symptom, which resolves by the age of 5<sup>3</sup>. Cough and congestion symptoms may occur episodically in otherwise healthy children<sup>9</sup>.

Infants who experience transient wheeze during early life, were shown to have significantly lower lung function than children who had no wheezing episodes during the first year of life<sup>10, 11</sup>. Low lung function was evident shortly after birth, before any lower respiratory tract illness had occurred<sup>7</sup>. However transient wheezers were as unlikely as children who did not experience preschool wheeze, to experience future wheeze<sup>10</sup>. Morgan et al concluded that both lung function and events such as LRTI and wheeze occurring in preschool years, determine the expression of asthma and level of lung function levels in childhood and adolescence<sup>10</sup>.

Contrastingly, using results from the reputable Tucson Study, Martinez et al found that wheezing in the first three years of life did not affect the child later in life<sup>12</sup>. They demonstrated that 60% of children who experienced wheeze before the age of three had stopped by the age of six despite a third of the children studied, experiencing wheeze<sup>11</sup>. Findings also suggested that most infants who wheeze have transient conditions associated with diminished airway function and experience no increased risk of asthma or allergies later in life.

A study by Brooke et al. found that while 6.7% of preschool children had started to wheeze, a significant proportion of those children (37.9%) continued to wheeze into their early school years<sup>13</sup>. The study also found 37% of children reported a recurrent cough and the proportion of these who began to wheeze was 7.2%<sup>13</sup>. In a study by Linehan (2005) however, the prevalence of wheeze and night time cough was shown to decrease over the period of the study from 35.4% (1993) to 29.1%(1995) and 40.2%(1999) to 30.8%(2001) respectively<sup>14</sup>. There were no substantial changes in the prevalence of hay fever, eczema, or family history of asthma<sup>14</sup>. The decreases in the prevalence of respiratory symptoms observed in this study may represent either a true decrease in symptoms, an improvement in treatment, or may be a reflection of changes in the prevalence of conditions other than asthma that cause symptoms in young children<sup>14</sup>.

Recognised predictors of wheeze in the first year of life include maternal smoking during pregnancy, low birth weight, prematurity, and lower respiratory infections such as bronchiolitis or pneumonia<sup>14, 15</sup>. Socioeconomic status and race/ethnicity are also predictors of early childhood wheeze, but these may simply indicate poorly defined environmental exposures<sup>15</sup>.

Asthma is the most common disease in childhood, affecting 10-15% of school age children in the UK<sup>13</sup>. Symptoms often start in early childhood but some preschool children will outgrow these symptoms so it is difficult to predict which children will develop asthma in later life<sup>3, 13</sup>. Frank et al identified exercise induced wheeze and a history of atopic disorders as predictors of the development of persistent respiratory symptoms in later childhood<sup>3</sup>. Although these factors are certainly a marker of asthma they do not predict a future diagnosis<sup>3</sup>. Results did however, support the findings of previous longitudinal surveys that reported atopy as a prognostic factor in the development of persistent respiratory symptoms<sup>3</sup>.



Frank et al concluded that using baseline exercise induced wheeze and a history of atopic disorders, it is possible to estimate a likelihood of future asthma in children with preschool wheeze<sup>3</sup>. The absence of a baseline exercise induced wheeze, in addition to atopic disorders reduces the chances of the child developing asthma by a factor of five<sup>3</sup>. These are important findings for both clinicians and parents particularly when planning future management<sup>3</sup>.

Adult methods for measuring respiratory function are difficult to use on young children, as a result, most of the physiological data natural history concerning wheeze in children is derived from children 6 years old or over<sup>13</sup>. Studies concluded that symptoms and respiratory function in mid-childhood are important when determining future outcomes<sup>13</sup>. The majority of work with regards to the respiratory symptoms of preschool children has been focused on the hospital-based populations rather than population-based samples<sup>13</sup>. The Manchester Asthma and Allergy Study (MAAS) found that at three years of age, interaction between maternal asthma and child's atopy was independently related to both cough and wheeze<sup>16</sup>. The study's results showed that lung function was related to symptom components independent of any interaction between child's atopy and maternal asthma, raising questions regarding potential underlying pathophysiological mechanisms<sup>9</sup>. However, by the age of five years the children's symptoms were not related to the child's atopic status<sup>9</sup>.

Pulmonary function tests enable health professionals to distinguish between healthy children and those with acute wheezing disorders<sup>17</sup>. They are however, unable to distinguish between wheeze phenotypes<sup>17</sup>. Lung function is assessed primarily by clinical parameters, such as history and symptom evaluation and functionally using spirometry<sup>17</sup>. Lung function tests include spirometry, bronchial challenge and peak flow<sup>13</sup>. As these methods are effort dependent, they are unreliable in children under the age of six<sup>13</sup>.

Results from a small Norwegian study suggest that spirometry using an animation program may be feasible in children aged 3–6 years, but it is time consuming and requires significant resources as children must be trained individually<sup>18</sup>. The study demonstrates a steady improvement in lung function levels with age, in addition to an improvement in the acceptability and reproducibility of lung function tests<sup>18</sup>.

Spirometric measures, such as peak expiratory flow and forced expiratory volume, also have apparent limitations when monitoring disease activity<sup>17</sup>. These problems can be avoided by using non-invasive measures that require minimal cooperation from the child such as a history or symptom evaluation using parental completed questionnaires<sup>13</sup>. Subsequently, preschool respiratory symptom questionnaires are an invaluable tool for exploring respiratory symptoms in a population in which object measures of lung function are difficult<sup>13</sup>.

## 1.2 Current Respiratory Symptom Questionnaires

Respiratory symptom questionnaires are invaluable tools in the exploration of occupational and respiratory health problems and associated risk factors, particularly in epidemiological studies<sup>19</sup>. Paediatric respiratory questionnaires for parental completion have demonstrated good repeatability but these questionnaires may not be appropriate for the younger preschool population<sup>9, 20, 21</sup>. Features commonly explored include wheezing, cough and breathlessness frequency<sup>9, 20, 22</sup>. Questionnaire responses have also been compared with clinical diagnoses and are a promising tool for recognizing respiratory conditions such as asthma<sup>23</sup>. The exposure, topics of interest or age group of the population determine respiratory symptom questionnaires used. Some are designed to predict respiratory diseases, monitor chronic conditions, or used as quality of life measures<sup>24-26</sup>. Many are validated for specific populations or specific diseases such as Chronic Obstructive Pulmonary Disease (COPD) or Asthma and some may be modified depending upon the outcome or exposure of interest<sup>27-30</sup>.

A literature search was conducted using MEDLINE®. Keywords searched include 'respiratory' 'symptom' and 'questionnaire'. The results were limited to studies published between the dates of 1991 and 2012. In total 775 articles were identified and reduced to 69 after reviewing titles and abstracts to determine relevance. The 69 articles related to 36 different respiratory symptom questionnaires for both children and adults and allowed identification of the most commonly used questionnaires in respiratory research. Questionnaires were recorded in two tables separating adult questionnaires from paediatric questionnaires. Through reviewing literature, a final 37 adult and 14 paediatric respiratory questionnaires were identified (see appendix 1, tables 8.2 and 8.3).

### 1.2.1 Adult Questionnaires

Adult respiratory symptom questionnaires primarily focus on monitoring chronic conditions or assessing health-related quality of life<sup>31, 32</sup>. They are invaluable tools for assessing respiratory epidemiology particularly within the community and occupational groups. Questionnaires commonly used in adults include the St George Respiratory Questionnaire (SQRQ)<sup>31</sup>, the American Thoracic Society Standardized Respiratory Questionnaire (ATSq)<sup>33</sup>, the Global Allergy and Asthma European Network Questionnaire (GA2LENq)<sup>34</sup> and the Medical Research Council (MRCq) respiratory symptom questionnaire. The most commonly used questionnaires in the studies identified by the literature search are the SQRQ, modified versions of the ATSq and the MRCq<sup>35</sup>. Many studies have edited existing questionnaires to include additional questions on smoking, occupational hazard and various other exposure or occupational respiratory hazards<sup>36</sup>.

One of the first questionnaires widely used in adult epidemiological research is the British MRCq<sup>37</sup>. Either in its original format or as slightly modified version, it is probably the most widely used respiratory symptom questionnaire<sup>35</sup>. Developed as a tool to study respiratory epidemiology in communities and occupational groups, by researchers at the Medical Research Council, UK, it has been in wide use for over 50 years<sup>35</sup>. The wheeze, cough, and chest illness questions however, lack appropriate independent criteria and have not been specifically validated<sup>35</sup>. Reproducibility is achieved by having the questions asked by an observer who had previously used the training manual and cassette<sup>35</sup>. However, a version for self-administration is also available<sup>35</sup>.

The St George's Respiratory Questionnaire is designed to measure and quantify health status in adults with asthma and chronic airflow limitation<sup>31</sup>. It is also valid for use in bronchiectasis patients<sup>38</sup>. This questionnaire, designed for self-completion, consists of 50 items and 76 weighted responses that are divided into three components: symptoms, activity, and impacts<sup>39</sup>. It addresses the affect of respiratory symptoms upon patient but not upon the family and may also be used to assess health related quality of life (HRQL)<sup>40</sup>.

The Wisconsin Upper Respiratory Symptom Survey (WURSS 44) is an illness specific quality of life instrument for measuring the negative effects of the common cold in adults<sup>41</sup>. It includes questions on whether the person's cold has affected their daily activities, work inside and outside their home, their interaction with others and their personal life<sup>41</sup>. This questionnaire faces numerous limitations including those of self-assessment, understanding and response among different individuals and the difficulty interpreting scales not tied to universally understood reference standards<sup>41</sup>. However this tool has been validated to some extent and since has been used in numerous studies and clinical trials<sup>42-44</sup>. Additional cold questionnaires include the Jackson Cold Scale<sup>45</sup>.

The Living with Asthma Questionnaire is an additional illness specific quality of life measure, designed for asthmatic adults<sup>32</sup>. It explores the impact asthma has upon the person completing the questionnaire, however it does not assess the impact of the patient's illness upon their immediate family<sup>32</sup>. Additional asthma specific questionnaires include the Asthma Quality of Life Questionnaire<sup>46</sup>, the Integrated Therapeutics Group Asthma Short Form<sup>47</sup>, the Asthma Control Questionnaire<sup>48</sup> and the Tasmanian Asthma Survey Questionnaire<sup>49</sup>. Additional asthma and allergy questionnaires include the questionnaire used to investigate the occurrence of allergies, asthma and other lung diseases in Hordaland<sup>50</sup>, the New Finnish Respiratory Questionnaire<sup>51</sup>, the Tuohilampi Questionnaire<sup>52</sup>, the Global Allergy and Asthma European Network Questionnaire<sup>34</sup>, and the Respiratory and Allergy Focused questionnaire<sup>53</sup>.

Illness specific measures of chronic respiratory symptoms have been developed for conditions such as COPD<sup>28, 54</sup>, pneumoconiosis<sup>55</sup>, cystic fibrosis<sup>56</sup>, tuberculosis<sup>57</sup>, chronic bronchitis<sup>58</sup> and emphysema<sup>59</sup>. These are particularly useful tools as they have been validated to monitor these conditions in a non-invasive manner. Quality of life measures provide a valuable insight into the impact of these conditions upon the patient.

A number of adult respiratory questionnaires have been developed to explore the relationship between smoking, occupational health hazards or climate conditions. Occupational and environmental questionnaires include the Orebro Indoor Climate Questionnaire<sup>60</sup>, the Environmental Symptom Questionnaire<sup>61</sup>, the Adult questionnaire used in the Arizona Tucson Epidemiologic Study of Obstructive Lung Diseases<sup>62</sup> and the Questionnaire of the European Community for Coal and Steel on respiratory symptoms<sup>63</sup>. Questionnaires that explore the effect of smoking include the questionnaire used in the Cooperative European Anti-Smoking Evaluation Questionnaire<sup>64</sup>, and the Cough Quality of Life Questionnaire<sup>65</sup>.

### 1.2.2 Paediatric Questionnaires

The most commonly used questionnaires available specifically for children include the International Study of Asthma and Allergies in Children (ISAAC) questionnaire for ages 6 years to 13 years<sup>66</sup> and the Test for Respiratory and Asthma Control in Kids (TRACK)<sup>67</sup>. Both questionnaires have been validated by numerous studies and have been shown to effectively measure respiratory symptoms in children<sup>67, 68</sup>.

Although the ISAAC questionnaire is widely used it has not been validated in the preschool population<sup>66</sup>. Numerous questionnaires exist that are designed to make tentative diagnosis, monitor chronic respiratory diseases and also recognise severity of acute respiratory conditions<sup>47, 69</sup>. In a population where parental observation is essential due to the limitations of paediatric histories, these questionnaires are invaluable<sup>47</sup>. However, parental recall is a limiting factor to consider when interpreting these questionnaires for younger children<sup>14</sup>. In order to combat this many paediatric questionnaires, particularly in the older age group have been designed to be completed by the child<sup>68</sup>. Respiratory questionnaires are particularly valuable in the paediatric population as there is a lack of objective measures of pulmonary function and symptom similarity in common childhood illnesses<sup>66</sup>.

TRACK has been shown to be a valid, caregiver-completed questionnaire that assesses respiratory control in preschool children with symptoms of asthma<sup>67</sup>. During the development of this tool, control status was correctly classified in as many as 81% and 78% of cases<sup>67</sup>. Studies advertise TRACK as a valuable aid to monitor young children with symptoms consistent with asthma, particularly in a population where this is difficult to assess via other methods<sup>67</sup>.

The ATS – DLD-78-C version of the Children’s Questionnaire has been tentatively recommended as a standard questionnaire for studies of children ages below 13 years in epidemiological studies by authors of *‘recommended respiratory disease questionnaires for use with and adults and children in epidemiological research’*<sup>70</sup>. The committee that recommended this questionnaire believe that considerable further field-testing of the questionnaire is needed which could lead to modification of the questionnaire<sup>70</sup>. This questionnaire is designed for use in the under 13-age group and may be self administered or interviewer administered. Authors of this questionnaire noted that wheezing; independent of diagnosis of asthma appears to be an important predictor of poorer pulmonary function<sup>70</sup>.

The Paediatric Asthma Quality of Life contains 23 items that children with asthma identified as troublesome in their daily lives<sup>71</sup>. It aims to examine the burden of illness experienced by children with asthma<sup>71</sup>. This questionnaire is divided into three domains; activity limitation, symptoms and emotional function<sup>71</sup>. A study assessing measurement properties showed that the tool was able to detect change in patients who improved and deteriorated, was able to distinguish such patients from those who remained stable and showed a high index of responsiveness<sup>71</sup>. The Integrated Therapeutics Group Child Asthma Short Form (ITG-CASF), originally developed by Usherwood et al, is an additional parental completed questionnaire designed to measure symptoms and disability in asthmatics aged 5-14 years<sup>72</sup>. It was developed by experienced general practitioners with involvement from mothers and asthmatic children<sup>72</sup>.

The Cystic Fibrosis Questionnaire is a disease specific instrument that measures health related quality of life in patients with Cystic Fibrosis<sup>56</sup>. Two validated versions exists, one for the adolescent and adult population (aged > or =14 years)<sup>73</sup> and one for the paediatric population aged 8 to 13 years<sup>56</sup>. The paediatric CFQ Child P is designed for child or parent completion and enables the assessment of CF and treatment impact on the patient’s Quality of Life (QoL) and health status<sup>56</sup>.

### 1.2.3 Studying Preschool Respiratory Symptoms

Few targeted respiratory questionnaires exist for the preschool population. Many are designed from existing questionnaires for children that may not be suitable for the preschool age group where symptoms may differ due to changing development<sup>74</sup>. The limitation of speech with severe wheeze and exercise-induced symptoms cannot be assessed in infants unable to talk and run so standard questionnaires for school children cannot automatically applied to infants or very young children<sup>74</sup>.

Luyt et al (1994) designed their own questionnaire for use in one to five year olds. Questions focused on wheezing and wheeze attacks with some emphasis on running induced wheezing<sup>20</sup>. Their questionnaire was designed because there was no suitable or well-validated questionnaire identified for this age group<sup>20</sup>. Questions were taken from previously validated questionnaires where possible<sup>75</sup>. The questionnaire may be divided into 3 sections with a total of 51 questions<sup>20</sup>. Sections dealt with:(1) The nature of respiratory history and symptoms wheeze, cough, and doctor diagnosed asthma (2) putative environmental factors, and (3) family's social status and history of atopy<sup>20</sup>. All questions seemed to have face validity, and informal tests of construct validity showed no serious inconsistency between the results of related questions<sup>20</sup>. The questionnaire by Luyt et al is able to define the severity of wheeze, and number of attacks of wheeze in 12 months, but none of the questions examine the impact of the wheeze attacks on the child and the family<sup>75</sup>.

The Boston Prospective Birth Cohort Study administered a questionnaire regarding home characteristics, home environmental exposures (including smoking) and demographic and socioeconomic characteristics of the family<sup>15</sup>. Trained research assistants were needed to administer this questionnaire during home visits<sup>15</sup>. This birth cohort only recruited mothers who answered yes to any of the following questions: (1) Have you ever had a doctor's diagnosis of asthma, hay fever, or allergies.



(2) Has the biological father of your child ever had a doctor's diagnosis of asthma, hay fever, or allergies<sup>15</sup>. Authors noted that this method of assessing preschool respiratory symptoms has not been validated<sup>15</sup>.

Strippoli et al also designed their own postal questionnaire for one-year-old children for use in cross-sectional and large population-based longitudinal studies and future community based studies<sup>74</sup>. This is a short, four-page questionnaire that could be posted to families with young children, for self-administration to parents<sup>74</sup>. This questionnaire was assessed for test-retest repeatability, a measure of the consistency of the performance of a questionnaire when used under similar circumstances<sup>74</sup>. Repeatability was shown to be excellent for sections on family history and environmental exposures, good for questions on wheeze, asthma, treatment and healthcare utilisation over the past 12 months, and moderate for upper respiratory symptoms and cough<sup>74</sup>. Although this questionnaire demonstrated good repeatability this does not necessarily mean it has good validity<sup>74</sup>.

The Wythenshawe Community Asthma Project (1993) also designed a questionnaire for preschool children, based upon the International Study of Asthma and Allergies in Childhood (ISAAC) study questionnaire<sup>76</sup>. This was a community study based at the Wythenshawe GP unit. Because the ISAAC questionnaire had not been validated as a tool for identifying asthma in one to four year olds, the study concentrated on the identification of respiratory symptoms that are likely to be markers of disease<sup>76</sup>. Follow-up response rates for this postal questionnaire were high at 72.8%, 70.6%, 65.0%, and 60.7% (1993, 1995, 1999, and 2001) respectively, but had some attrition over time (overall difference = -12.1%, 95% CI for the difference -8.0% to -16.2%)<sup>14</sup>.

The Manchester Asthma and Allergy Study (1995) is an unselected, hospital population-based birth cohort that used a validated respiratory questionnaires administered by an interviewer<sup>77</sup>. Questions were derived from the ATSq for children aged three<sup>78</sup>.

Additional questions were included from the ISAAC study for children aged five<sup>78</sup>. This study sought to investigate the relationship between genetic predisposition and environmental exposures in the development of atopy, asthma and other allergic diseases<sup>78</sup>.

Powell (2002) et al designed and developed the Liverpool Respiratory Symptom Questionnaire (LRSQ)<sup>79</sup>. It is a tool that aims to explore the prevalence and natural history of respiratory symptoms in infants and preschool children<sup>79</sup>. It may be used as a follow up tool for use in neonatal studies where the outcome at two to three years of age is of interest<sup>79</sup>. A unique feature of this tool is that, unlike many other respiratory questionnaires, it explores the impact of wheeze and other respiratory symptoms upon the child and their family<sup>79</sup>.

### 1.3 The LRSQ and Supporting Evidence

Numerous adult questionnaires explore the impact of respiratory symptoms upon the patient and their lives<sup>32, 38</sup>. However, apart from the LRSQ no preschool questionnaire for parental completion explores the impact of these respiratory symptoms on the children and their parents. There are currently very few respiratory questionnaires validated specifically for the preschool age groups<sup>14</sup>. A tool for parental completion, this standardised questionnaire has been developed over the course of the last decade using standard questionnaires already in use<sup>79</sup>. Six respiratory paediatricians provided their expertise to finalise the content of this questionnaire<sup>79</sup>. This tool explores the prevalence and natural history of respiratory symptoms in infants and preschool children and may be used as a follow up tool for use in neonatal studies where the outcome at two to three years of age is of interest<sup>79</sup>.

Furthermore, the questionnaire has shown potential as a valuable tool for assessing a three months snapshot of respiratory symptoms in preschool children and demonstrates potential as a tool for assessing and monitoring respiratory symptoms in preschool children with Cystic Fibrosis (CF)<sup>80</sup>.

A key feature of this tool is that it allows researchers to explore the burden of respiratory symptoms and respiratory disease within the community<sup>79</sup>. This is done by not only assessing the effect of respiratory symptoms upon the child but also the effect upon their family. Despite covering an extensive number of symptoms the LRSQ maintains acceptability<sup>79, 80</sup>.

Parents completing the LRSQ only report respiratory symptoms their child experienced over the preceding three months<sup>79</sup>. Authors have intentionally phrased questions so as not to include technical terms, leading questions, double negatives and use of words open to interpretation<sup>79</sup>. Symptoms reported are broken down into nine domains. Each domain contains between three to five items scored on a five point Likert Scale from “not at all” (score 0) to “every day” (score 4)<sup>79</sup>. The initial five domains cover respiratory symptoms over five periods that include daytime, night time, during colds, between colds and during activity. These five domains individually explore respiratory symptoms such as wheeze, cough, rattly chest and dyspnoea<sup>79</sup>. The sixth domain focuses on additional symptoms the child experiences, this includes noisy breathing not from chest, tachypnoea and noisy breathing from the back of the throat<sup>79</sup>.

A unique feature of this questionnaire is that it explores the impact of wheeze attacks and other respiratory symptoms on the child and their family in the final two domains<sup>79</sup>. These domains include questions about the child’s feeding/eating, sleep and activity in addition to parent’s sleep, activities and adjustments to family life<sup>79</sup>. A ninth domain was included in the initial development of the questionnaire<sup>79</sup>. This domain asks for details regarding medication, GP/clinic visits, hospital admissions and diagnostic “labels” given<sup>79</sup>. It aims to gather facts about treatment and interactions with health care services, the exclusion of this section does not affect the validity of the symptom component of the questionnaire.

**Table 1.1 Summary of the domains of the Liverpool Respiratory Symptom Questionnaire**

Domain	Respiratory Symptoms (last three months only)	Questions
1	Daytime symptoms	Wheezing, Cough, Rattly chest, Dyspnoea
2	Night-time symptoms	
3	No of colds, Symptoms during a cold	
4	Intermittent symptoms (between colds)	
5	During Activity	
6	Other	Noisy breathing not from chest, tachypnoea, noisy breathing from back of throat.
7	Effect on child	Feeding, waking, reducing activity, caused tiredness
8	Effect on Family	Limited activities, adjustment to family life, disturbed sleep and worry.
9	Other details	Treatment for respiratory symptoms and visits to the GP or hospital

The practicality, response rates, reliability (test–retest reliability and internal consistency) and validity (face and content validity and criterion validity) of this valuable tool have been assessed in two previous studies<sup>79, 80</sup>. Powell et al used a small cohort of 144 infants for initial exploration of the questionnaire but justify this as a reasonable number as previous study’s developing questionnaires have used similar figures<sup>79</sup>. The majority of questions were shown to have moderate to good short-term reliability with a weighted kappa score greater than 0.4<sup>79</sup>. However the question on “noisy breathing from the back of the throat” indicated only fair agreement with a kappa score of 0.39 so, after assessing reliability, authors recommended that it should be removed from any future revision of the questionnaire<sup>79</sup>.

Results by Powell et al on internal consistency of the questionnaire, showed that the question on snoring accounted for 3.7% of the variance; questions 17, 18, and 19, about fast breathing and noises coming from the throat, accounted for 4% of the variance and were subsequently removed prior to further analysis<sup>79</sup>. The four initial domains and internal consistency scores having excellent internal consistency<sup>79</sup>. Subsequently, each domain has items that are closely related and have good within-scale and between-item correlations<sup>79</sup>. Response rates were 64% initially, with repeat response rates of 56%, demonstrating satisfactory response rates when administered to a cohort of postnatally recruited subjects. Readability was not examined in detail so may affect response rates<sup>79</sup>.

Authors did not fully assess validity<sup>79</sup>. Criterion validity was identified as being difficult to assess, as there was no objective gold standard measure to compare with<sup>79</sup>. Respiratory physicians based diagnosis of asthma (RPBDA) was however coarsely used to assess this in an outpatient's cohort<sup>79</sup>. All eight of the scales in the questionnaire were shown to differentiate a child with a RPBDA from a well child<sup>79</sup>. All scores had acceptable sensitivity (between 88.9% and 96.7%)<sup>79</sup>. However, it has been suggested by Powell et al that a more detailed examination of the questionnaire with respect to criterion validity will require larger numbers of infants, with different phenotypes of wheeze compared against a different gold standard<sup>79</sup>. This initial study shows the questionnaire has strong construct validity and internal consistency with the eight concept domains used<sup>79</sup>. Resulting in a practical, acceptable respiratory symptom questionnaire that is easily completed, with good response rates and good repeatability<sup>79</sup>.

A cross-sectional study by Trinick et al, who used the questionnaire to explore respiratory symptoms in young children with Cystic Fibrosis<sup>80</sup>. This study aimed to assess if the LRSQ could distinguish between well children and children with stable CF in the preschool age group. In addition, Trinick examined the possibility of distinguish between 'well' and 'unwell' children with CF<sup>80</sup>. Patients were recruited during routine clinic appointments whilst healthy controls were recruited from local nurseries and schools or were children of members of staff or friends of patients admitted to Alder Hey Children's Hospital<sup>80</sup>. Due to this method of selection the control population recruited may not be an accurate representation of the cohort of interest<sup>80</sup>. This study also recorded CF children's Northern chest X-Ray scores, Shwachman score, spirometry results, *Pseudomonas* carriage, antibiotic usage and school attendance over the last 3 months<sup>80</sup>.

Trinick et al sought to further validate the questionnaire's external and internal validity<sup>80</sup>. Internal consistency was assessed using Cronbach's coefficients<sup>80</sup>. In six out of eight domains scores ranged between 0.76–0.89, demonstrating acceptable to good internal consistency<sup>80</sup>. Despite the 'night-time symptoms' domain having a coefficient of 0.64, if the question regarding snoring was removed this improved to 0.71<sup>80</sup>. The "cold symptoms" domain had a coefficient of 0.66<sup>80</sup>. Trinick et al were able to show that internal consistency was acceptable-to-good across all domains, demonstrating good internal validity while maintaining acceptability<sup>80</sup>. This study's results suggest that the LRSQ is a sensitive tool for detecting respiratory disease in the pre-school and school-age CF population<sup>80</sup>.

A small, unpublished cross-sectional study (2012) was also conducted using the Liverpool cohort<sup>81</sup>. This study aimed to assess the respiratory symptoms in infants four to nine years following exposure to Human Respiratory Syncytial Virus (hRSV) bronchiolitis using the LRSQ<sup>81</sup>. It also aimed to assess the validity of the questionnaire for use in the preschool population<sup>81</sup>. This study again demonstrated that the LRSQ has good internal validity using Cronbach's coefficient (8/9 domains ranged between 0.92-0.94)<sup>81</sup>. In addition, questionnaire design issues were identified providing a platform for improvements that may help with data collection and improve the clarity of the questionnaire<sup>81</sup>. These include reformatting the ninth domain with options included for open-ended questions such as an asthma diagnosis, in addition providing the child's name in question to avoid confusion. The study demonstrated that statistically significant and clinically meaningful results can be obtained even from a small cohort of 40 patients<sup>81</sup>.

A particular strength of this small, unpublished study is that it also explored the impact of the child's respiratory symptoms on the child and their family using the LRSQ<sup>81</sup>. Results for these domains were significantly different between controls and patient (mean scores ranged from 0.75 to 2.14 respectively,  $p < 0.001$ ). The study demonstrated that respiratory syncytial virus infection in infancy not only has a profound effect upon respiratory symptoms in later childhood but also impacts children's families<sup>81</sup>. This study also acknowledged that the LRSQ might have a use as a measure of longer-term respiratory status either in an annual review assessment or for longer, follow-up studies<sup>81</sup>. However, this has yet to be assessed in a larger longitudinal, epidemiological study.

## 1.4 Birth Cohort Studies

### 1.4.1 What are they?

Birth cohort studies involve multiple surveys of large numbers of individuals sharing similar characteristics from birth, throughout their lives<sup>82</sup>.

Information regarding education, employment, family circumstances, parenting, physical and mental health, and social attitudes is collected and collated<sup>82</sup>. Of all the methods used for epidemiology research, the long-term cohort is particularly important<sup>83</sup>. It is the best method for identifying the incidence and natural history of a disease<sup>82</sup>. These longitudinal studies can be used to examine multiple outcomes after a single exposure are able to show how demographic and exposures such as health, wealth, education, family and employment are interwoven for individuals fluctuate, affecting single or multiple outcomes or achievements in later life<sup>83</sup>.

The potential of these studies as a valuable research tool is clear, particularly within epidemiology<sup>83</sup>. Although randomised controlled trials are usually regarded as the gold standard for tackling research questions, there are times when they are either impossible or simply unethical to use e.g. when testing the effects of harmful or dangerous exposures e.g. tobacco smoke<sup>83</sup>. Following people for several years, particularly a lifetime, provides a chance to explore their development, health and ageing in relation to changes in their personal circumstances or the wider economic and social environment<sup>83</sup>. While simple in principle, this is not easy in practice. Large cohort studies need sizeable populations in order to yield significant results<sup>83</sup>. They take considerable time and absorb a vast amount of resources<sup>83</sup>.



### 1.4.2 Critical Appraisal of Birth Cohort Study Design

In order to evaluate the casual mechanisms of respiratory disease and describe the respiratory symptoms of preschool children, an observational analytical study was deemed necessary. An observational analytical study enables a description of respiratory symptoms experienced by the Liverpool preschool population by observing respiratory symptoms using answers provided from the questionnaire. It also enables researchers to quantify any potential relationships between factors such as respiratory symptoms and an exposure.

Observational study designs include case-series, cross-sectional and cohort studies. Case series studies describe a group of subjects with a similar diagnosis or feature identified at the start of the study, this method is unable to study cause and effect relationships and is not suitable for the LRBCS. Cross-sectional cohort studies are able to indentify associations between variables but they are unable to establish casual sequences as they do not follow subjects longitudinally over time, but instead take 'snapshots' at specific time intervals.

Despite the cross-sectional study being a cheaper alternative, a cohort study is the most appropriate for the LRBCS as it enables the description of respiratory symptoms over time and the identification of associations between exposures and the outcome measures. Prospectively cohort studies are also able to establish casual sequences and the incidence of disease. Additional strengths are that several outcomes may be studied for each exposure, such as the different domains of the questionnaire. However cohort studies are notable expensive and time consuming and carry a high risk of attrition so this must be taken into account in the study design and during analysis.

### 1.4.3 National British Birth Cohort Studies

There are four world-renowned, key British longitudinal studies that are all on-going. As valuable contributors to epidemiological research, they have provided a wealth of data regarding British health and social issues during maternal, childhood, adulthood and the older years and continue to do so.

#### **1. MRC National Survey of Health & Development (NSHD) (1946)<sup>84</sup>**

Not only the oldest of the British birth cohort studies, the NSHD is the most unique as data has been collected from participants from birth to the age of 65<sup>84</sup>. All mothers who had a baby between the third and ninth of March, 1946 in England, Scotland or Wales were interviewed by health visitors, eight weeks after birth<sup>84</sup>. From an initial maternity survey of 13,687 of all births recorded, a socially stratified sample of 5,362 singleton babies born only to married parents were selected for follow up<sup>84</sup>. The study initially aimed to address health and social policy questions which were: “why the national fertility rate had been falling consistently since the middle of the 19<sup>th</sup> century”, “what was the national distribution and use of obstetric and midwifery services and how far do they prevent premature and infant death and promote the health of mothers and infants”<sup>84</sup>. A total of 22 surveys have been conducted since recruitment from participants who are now in their mid sixties<sup>84</sup>. Numerous studies have been conducted using the data, with many on going that relate to aging research<sup>85-88</sup>.

Childhood illnesses, poor social circumstance and atmospheric pollution have been shown to increase the risk of lower respiratory problems in adulthood<sup>89</sup>. In addition, smoking was shown to independently exacerbated these early life risks<sup>89</sup>. The risk of respiratory disease at the age of 2 years was associated with overcrowded and poor home circumstances and those who suffered such respiratory illness in childhood had a higher risk of developing chest disease as adults<sup>84, 89</sup>.

Strengths of this study include the large sample size and intensive phenotyping<sup>84</sup>. An additional strength is that data collection was performed during home visits, generally by the same research nurse team if the study member could not attend the clinic<sup>84</sup>. Study authors claim this will help to maintain the representativeness of the NSHD study sample against the social and health bias associated with attending the clinic<sup>84</sup>. One general benefit of longitudinal studies is that bias in the remaining sample can be identified and taken into account before generalizing to the UK population of the same age<sup>84</sup>. The duty of care protocols involved a survey doctor and ensured participants were appropriately referred to their GP if needed<sup>84</sup>. This programme, developed specifically for an older population, reassured participants, facilitated their retention in the study and ensured appropriate clinical follow-up where necessary<sup>84</sup>.

Limitations included a one-week recruitment period, which is likely result in an inaccurate representation of the population, particularly with regards to ethnicity and social demographics. In addition, only infants born to married parents were recruited which adds to the inaccurate representation of the population. Additional limitations include a long period of data collection, maintaining staff skills, dealing with staff turnover, servicing and technical updates of equipment, keeping morale high and costs contained<sup>84</sup>. Study length was determined by funding requirements. In order to undertake a comprehensive health assessment on a scattered geographical sample the team were required to set up six data collection centres which presented numerous opportunities for error<sup>84</sup>.

## **2. *National Child Development Study (NCDS), 1958***<sup>90</sup>

This study began as a study of perinatal mortality but has evolved into a continuing birth cohort study<sup>90</sup>. The findings contributed to an improvement in maternity services in Britain, thus reducing perinatal mortality, and particularly the rate of stillbirths<sup>90</sup>. The study aimed to recruit all babies born in England, Scotland and Wales during one week in March 1958<sup>90</sup>. Almost 17,500 babies were recruited, but it was noted that this cohort did not match the ethnic diversity of today's population<sup>90</sup>. Key findings and publications from this study were primarily regarding social and health inequalities<sup>90</sup>. One important finding was that reductions in birth weight were linked to maternal smoking, particularly in the second and third trimester<sup>91</sup>. Cigarette smoking during pregnancy was shown to increase the late foetal and neonatal mortality rate by 28% and reduced birth weight by 170g. These results were independent of factors such as maternal age, weight and height and socioeconomic position (determined by the father)<sup>91</sup>. Higher rates of spontaneous abortion were reported amongst smokers<sup>91</sup>. Studies of wheezing symptoms and asthma showed that of children with symptoms before the age of 7, 50% had attacks during the previous year and 35% had complete remission by early adulthood<sup>92</sup>. As many as 5% of children had persisted symptoms whilst the remainder experienced intermittent symptoms<sup>90, 92</sup>. Incidence of asthma and atopy were strongly influenced by atopy and smoking<sup>92</sup>. Participants with a history of pneumonia in early childhood had lowered FEV1 and FVC levels at 34-35 years that was not reversed by salbutamol<sup>90, 93</sup>. The study provided one of the first data sets that allowed the study of obesity<sup>90</sup>. One study concluded that children of obese and overweight parents have an increased risk of obesity thus providing a platform for future research<sup>94</sup>. The large cohort used in the NCDS provides a wealth of data in addition to adding weight to the data<sup>79</sup>. However similar to the NSHD, participants were recruited over a period of one week<sup>90</sup>. Recruitment over such a short period may not provide an accurate representation of the population with regards to ethnicity and demographics. It also does not account for seasonal variance that can occur with some diseases<sup>90</sup>.

### **3. 1970 British Cohort Study (BCS70)<sup>95</sup>**

This is an on-going, longitudinal study that was originally named the British Births Survey. All babies born between the 5<sup>th</sup> and 11<sup>th</sup> of April 1970 in England, Scotland, Wales and Northern Ireland were recruited<sup>95</sup>. Since the initial birth survey, there have been seven full data collections of the 17,000 person cohort in order to monitor participant's physical, educational, social and economic development<sup>95</sup>. Data was collected using a questionnaire completed by the midwife present at birth and also extracted from clinical records<sup>95</sup>. During childhood, cohort members were traced through schools and immigrants born in the reference week were also recruited<sup>95</sup>. The study aimed to compare its results with those of the NCDS (1958)<sup>95</sup>. Like the NCDS the focus of the BCS70 was on the medical management of pregnancy and birth<sup>95</sup>.

A number of studies using the data from this cohort focused on maternal smoking during pregnancy<sup>95-97</sup>. Maternal cigarette smoking was found to be significantly associated with a decreased birth weight and these results reflected those from the NCDS<sup>95</sup>. Low birth weight, independent of maternal smoking, was identified as a risk factor for febrile convulsions and afebrile seizures in children up to the age of ten<sup>98</sup>. An increased risk of perinatal mortality of smokers offspring in the manual social class was also noted<sup>98</sup>. Maternal smoking was also found to increase the incidence of respiratory illnesses in children, including admission to hospital for lower respiratory tract diseases during the first five years of life<sup>99</sup>. Longer-term impacts of maternal smoking include an increase in offspring smoking at age 16<sup>95</sup>. Furthermore, an increase in psychological and somatic distress at age 26<sup>95</sup>. An overview of cross-cohort comparisons showed a reduction in adults smoking in their 30s particularly among women, but an increase in alcohol consumption and illegal drug use<sup>95</sup>.

Several studies exploring asthma risk factors have shown that childhood wheezing illness is not only related to maternal smoking and low birth weight but also to preterm birth, male sex, low maternal age and early introduction of bottle-feeding, particularly by the age of 5<sup>100</sup>. Most wheezing illness occurring in early childhood resolved by adolescence<sup>100</sup>. Although symptoms may have recurred at a later date, most childhood wheeze had a good prognosis<sup>100</sup>. Childhood wheezing may comprise of more than one disease, the majority occurring in response to viral infections, and the minority as a result of allergic asthma<sup>100</sup>. However, it was not possible to separate the effects of maternal smoking during pregnancy from the effects of passive smoking in infancy, because most mothers who smoked during pregnancy continued to smoke during the neonatal and infant period<sup>100</sup>.

Other studies specifically focused upon the impact of breast feeding on subsequent health outcomes such as eczema and hay fever, bronchitis, lower respiratory illness, and gastro-enteritis<sup>101</sup>. Associations between breast feeding and developmental outcomes for children were examined in addition to a link between socio-economic status and infant health<sup>101</sup>. Lack of funding at time inhibited development of strategies<sup>95</sup>.

Strengths of BCS70 include a large cohort that provides an extensive array of data, a multi purpose design and extensive data coverage at seven time points<sup>95</sup>. The longitudinal design enabled the assessment of long-term correlates of health conditions and disease in childhood<sup>95</sup>. It also provides the opportunity to investigate which risk factors in childhood are the best predictors of adult health conditions<sup>95</sup>. Limitations are that recruitment took place during a single week, so the cohort may not accurately represent the general population in the 1970's<sup>95</sup>. In addition the team report difficulties recruiting immigrants and that problems with funding inhibited the development of some strategies<sup>95</sup>.

#### **4. Millennium Cohort Study (MCS), 2000<sup>102</sup>**

This study follows the lives of around 19,000 children born in the UK between 2000-2001 and is the most recent of Britain's national longitudinal birth cohort studies<sup>102</sup>. It is also the first national birth cohort study for 30 years and the fourth of Britain's world-renowned longitudinal birth cohort studies<sup>102</sup>. It involves children born in England, Wales, Scotland and Northern Ireland over a 12-month period<sup>102</sup>. The sample of births was stratified to disproportionately over represent areas with high proportions of ethnic minorities and areas of high child poverty<sup>103</sup>. Five surveys of the cohort members have been conducted so far, the most recent took place in 2012<sup>104</sup>. This is a government initiated study to mark the millennium and the objectives were laid down in the Centre for Longitudinal Studies' proposal to the Economic and Social Research Council (ESRC) in March 2000<sup>102</sup>. It aimed to chart the initial conditions of social, economic and health advantages and disadvantages of children born at the beginning of the 21st century<sup>102</sup>. This would facilitate an understanding of the origins of social exclusion and to contribute to the development of a number of policies with regards to education, health, parenting and employment<sup>102</sup>. Families were interviewed when eligible babies were 9 months old, to establish conditions from which they set out in life<sup>102</sup>. The sample of births in this cohort were taken over a period of a year with babies identified from electoral wards<sup>102</sup>.

Results remonstrated that breastfeeding, particularly when exclusive and prolonged, protects against factors that cause hospitalisation, subsequently influencing morbidity in contemporary United Kingdom<sup>105</sup>. The study concluded that a population-level increase in exclusive, prolonged breastfeeding would considerably benefit public health<sup>105</sup>. Exclusive breastfeeding particularly protects against hospitalization for diarrhoea and lower respiratory tract infections<sup>105</sup>. Asthma, wheezing or whistling in the chest in the preceding 12 months were more common in children from disadvantaged communities in all four UK countries<sup>106</sup>. Asthma and wheezing was also significantly more common among children whose mothers had smoked in pregnancy<sup>106</sup>.

Children growing up in disadvantaged areas were more likely to experience disability and ill health<sup>107</sup>. These include problems with vision, hearing and longstanding conditions such as asthma, chronic infections and injuries<sup>107</sup>. In addition, children were also shown to be at an increased risk of being obese or overweight<sup>107</sup>. Studies looking at ethnicity and respiratory disease showed that Black Caribbean children were 70% more likely than their white peers to have had asthma by age three and 40% more likely to have wheezed in the last year<sup>107</sup>. Only half of this effect was explained by social and economic factors<sup>107</sup>. Contrastingly, Bangladeshi children were less likely to have ever experienced asthma or wheeze in the last year than white children<sup>107</sup>.

Strengths of this cohort include a large sample size that authors claim is representative of contemporary UK, particularly as recruitment took place over one year<sup>102</sup>. However, despite a longer recruitment period, the sample was tightly clustered geographically. It was also disproportionately stratified to over-represent areas with high proportions of ethnic minorities in England, areas of high child poverty and the three smaller countries of the UK respectively<sup>102</sup>. However authors claim that this disproportionately stratified design ensures adequate representation of these populations<sup>102</sup>.



#### 1.4.4 Regional British Birth Cohort Studies

Numerous past and on-going regional Birth Cohort Studies exist and these have been summarised in table 8.1 in appendix 1. British regional birth cohort studies have been set up to explore numerous factors and aid strategy planning for improving health care not only for health authorities but for the benefit of the whole country.

##### 1.4.4.1 Leicester Respiratory Cohort (1990)<sup>108</sup>

The Leicester Respiratory Cohort was established in 1990 and initially recruited a sample of 1,650 children born between 1985 and 1990<sup>108</sup>. A second cohort of 8,700 children born between 1993 and 1997 was recruited in 1998, this time using a stratified sampling design as the initial cohort was too small and did not include ethnic groups<sup>108</sup>. The purpose of this study was 'to study the childhood epidemiology of wheezing disorders and other common respiratory problems such as chronic cough, chronic rhinitis and habitual snoring'<sup>108</sup>. Questions asked were derived from the ATS childhood questionnaire and an adapted validated preschool questionnaire by Clifford et al<sup>22</sup>. In the second round the edited questionnaire administered to 1 year olds also included questions from ISAAC<sup>108</sup>. Response rates to the 1992 cohort were 86.2% to the initial survey but dropped to 57.3% in 2003<sup>108</sup>. Results showed that responses were better from participants of white ethnicity and a higher socioeconomic status but with a lower frequency of symptoms thus missing children from deprived areas<sup>108</sup>.

Results from this cohort, like many other cohort studies have public health implications<sup>108</sup>. Studies showed that the prevalence of wheeze doubled in the eight years between the two cohort samples<sup>109</sup>. Studies described the natural history of wheeze in this particular cohort and found that less than half of children who wheezed during preschool years continued to do so at early school age, and displayed features of asthma<sup>13, 109</sup>. South Asian women who migrated to the UK at the age of five years or older were shown to have a lower risk of asthma than those born in the UK or who migrated before age five<sup>109</sup>. This strongly supports the hypothesis that early life

environmental factors influence the risk of adult asthma<sup>109</sup>. Traffic air pollutant was associated with chronic cough and increased incidence of wheeze and cough in young children, and was shown to be dose related and independent of potential confounders<sup>108, 109</sup>. As many as 19% of preschool children used inhalers but a relative under-treatment of severe wheeze was demonstrated, in contrast to an over treatment of mild episodic wheeze and chronic cough<sup>108, 109</sup>.

#### **1.4.4.2 Isle of Man Cohort (1991)<sup>110</sup>**

The Isle of Man Cohort was invited to join the European Longitudinal Study of Pregnancy and Childhood (ELSPAC), a longitudinal study of child health, growth and development<sup>110</sup>. It involved approximately 40,000 children in eight European centres, one being the Isle of Man and was designed and coordinated by the Department of Child Health at the University of Bristol and promoted by the World Health Organisation<sup>111</sup>. It aimed to collect information about each child's background, birth and upbringing, to determine which factors are important in ensuring that each individual reached their maximum potential of health, growth and development<sup>110</sup>. Piloting this study revealed that a personal touch to recruitment was the most effective<sup>110</sup>. Using this method, an impressive recruitment rate of 97% was achieved using a research midwife<sup>108</sup>.

The return rate for child focused questionnaires for parental completion at six months was 54.6%, these figures remained relatively stable before dropping to 29.8% at seven years<sup>108</sup>. Interestingly, response rates rose significantly to 79.8% at 15/16 years when the children themselves completed questionnaires<sup>108</sup>. Results from the cohort were compared to those from the Avon study on mainland Britain<sup>112</sup>. Principal findings showed that the islands children have greater birth weights of >140g heavier than expected from their mainland counterparts<sup>108</sup>. This increase continued into childhood, resulting in a markedly increased body mass index (BMI) at the age of seven years<sup>108</sup>. A weakness of the study is that not all of the data has been analysed due to a lack of funding, despite having been collected and keyed<sup>108</sup>.

The study covers children born to all eligible mothers living on the island and includes similar, or identical questions to the ALSPAC and collects unique information about island population<sup>108</sup>. Two communities exist on the island, the native Manx population and those who migrated to the island<sup>108</sup>. Nevertheless, there is a high migration rate off the island and overall, this study includes a small cohort in comparison to other birth cohorts<sup>108</sup>.

#### 1.4.4.3 ALSPAC (1991)<sup>113</sup>

The Avon Longitudinal Study of Parents and Children (ALSPAC) was established to further an understanding of the genetic and environmental characteristics that influence the health and development of children and their parents<sup>114</sup>. Women resident within three health administrative districts in the South West of England, with an expected delivery date between April 1991 and December 1992 were recruited<sup>114</sup>. The majority of women (82%), expected to deliver between these dates, were invited to enrol<sup>114</sup>. This amounted to 13,761 women in total who were followed up over the last 19 to 22 years<sup>114</sup>. There were 68 data collection time points between birth and 18 years of age. Data included, questionnaire results and samples for genetic analysis<sup>114</sup>. Routine antenatal and maternity health services promoted the study and distributed an 'expression of interest' card, the return of which enables mothers to request further information or to decline participation<sup>114</sup>. Response rates decreased over time, particularly when collecting responses from young adults<sup>114</sup>.

Findings have had a significant impact on developing and changing health and social policies regarding cot death, risks for allergy in children and fish consumption during pregnancy<sup>114-117</sup>. Many studies also explored the socioeconomic position in life<sup>99, 106</sup>. Genetic research has described the filaggrin gene on children susceptible to eczema and asthma<sup>118</sup>. In addition, this study described the FTO gene that is associated with increased adiposity and consequentially, predisposition to obesity<sup>119, 120</sup>.

Environmental studies exploring the antenatal incidence of asthma, demonstrated factors that influence its development to childhood asthma that included prenatal maternal anxiety, paracetamol use, exposure to cleaning products and excessive hygiene regimes<sup>121-124</sup>. Similar to other birth cohort studies, one of the main strengths of this study is its general population base and sample size<sup>114</sup>. Despite this it lacks the power to study rare exposures and outcomes<sup>113, 114</sup>. An over representation of the more affluent groups and under representation of the non-White minority ethnic groups compared with the national population has occurred due to the demographic profile of the cohort and subsequent differential attrition<sup>114</sup>.

#### **1.4.4.4 Born in Bradford (2007)<sup>125</sup>**

The Born in Bradford Cohort (2007-2011) was established to examine genetic, nutritional, environmental, behavioural, and social factors that impact health and development during childhood and subsequently adult life<sup>125</sup>. It was created in response to worryingly high rates of childhood morbidity and mortality in Bradford. In total, 11,396 mothers completed the initial questionnaire<sup>125</sup>. Sixty percent of babies born in Bradford are born into the poorest 20% of the population of England and Wales based on the governments Index of Deprivation<sup>125</sup>. As a largely bi-ethnic cohort that included families of White British and Pakistani origin, this study was able to make comparisons between health and socioeconomic differences of mothers and babies from both ethnic groups<sup>125</sup>. Marked differences were seen between the birth weight of Pakistani origin and white British origin babies as the Pakistani babies were on average 200g lighter at birth<sup>126</sup>. One point to note is that researchers have demonstrated that embedding research in clinical practice with routine measurements taken by clinical staff, improves quality and expansion of the growth data collected<sup>125</sup>. This method promotes public health, data collection, the involvement of clinical staff and awareness of evidence based medicine<sup>125</sup>.

Difficulties engaging with fathers and partners were reported at both hospital and community events<sup>125</sup>. Despite the study obtaining the backing of community leaders, only 20% of partners or fathers enrolled in the study<sup>125</sup>. This only highlight the lack of opportunities to approach men, particularly as many do not attend clinics with their partners or are not in the house during home visits<sup>125</sup>. However, once approached >90% fathers consented to take part<sup>125</sup>. This is a recognised gap evident in many birth cohort studies<sup>125</sup>.

Recruitment at the end of the second trimester meant that early pregnancy exposures were not collected<sup>125</sup>. Language and literacy variation may lead to different exposures collected and differences in measurement error<sup>125</sup>. Key strengths of this study were the multidisciplinary background of researchers involved, in addition to close links with other national and international birth cohorts<sup>125</sup>. Although the large bi-ethnic cohort is representative of the population of Bradford, it is not representative of the UK population due to unusually high levels of poverty and diversity<sup>125</sup>.

#### **1.4.5 National and International Birth Cohort Studies**

Studies that include a minimum of 1000 recruits have been summarised in appendix one, table 8.1. The Tucson Study<sup>62</sup> and European Longitudinal Study of Pregnancy and Childhood (ELSPAC)<sup>127</sup> are discussed further in the chapter. Additional national studies to note include the Danish National Birth Cohort<sup>128</sup>, the Norwegian Mother and Child Birth Cohort Study<sup>129</sup> and the American Generation R Study<sup>130</sup>.

#### **1.4.5.1 Tucson Children's Respiratory Study (1980)<sup>131</sup>**

Set in Tucson, Arizona in the US, this reputable study followed 1,246 children and their families from birth<sup>131</sup>. It began as a national, longitudinal birth cohort study that aimed to examine the relationships between a large number of potential risk factors for acute lower respiratory tract illnesses during the first three years of life, in addition to the development of chronic lung disorders, especially asthma, in later childhood and young adult life<sup>131</sup>. In 2003, 78% of original recruits were still being followed<sup>131</sup>. Strengths include the collection of extensive pre-LRI data and data regarding risk factors in addition to extensive microbiology, virology, and serology data<sup>131</sup>. Furthermore, this study benefits from a long follow-up period with a good retention rate from a large, predominantly outpatient population cohort<sup>131</sup>.

One of the most important findings by the Tucson study is that events occurring early in life appear to be important determinants of subsequent asthma<sup>131</sup>. It was also found that 60% of children diagnosed with an LRI in early life reported no wheezing episodes by the age of six and later showed that the majority of these children remained asymptomatic by the age of 11 and 16<sup>131</sup>. This supports the hypothesis that diminished lung function at birth could explain the link between LRI and deficits in Spirometric parameters later in life<sup>132</sup>. However, children who did wheeze during an LRI in early life and were still wheezing at age 6, did not fit this hypothesis<sup>132</sup>. Their levels of lung function were slightly lower after birth but were significantly reduced by the age of six<sup>132</sup>. Risk factors identified for wheeze were low levels of lung function before any LRI develops, maternal smoking during pregnancy and younger mothers under the age of 30<sup>133</sup>. Breast-feeding of at least 1 month was associated with lower rates of wheezing LRIs during the first 4 months of life<sup>131, 134</sup>.

Furthermore, 60% of persistent wheezers were skin test positive to at least one aeroallergen by age six years, compared to less than 20% for non-wheezers<sup>132</sup>. Results concerning IgE production suggest that in a proportion of persistent wheezers, activation of the immune system towards IgE production could have occurred as early as the first year of life<sup>131, 132</sup>. IgE in umbilical cord blood showed no relation to later asthma, whilst the presence of IgE near the end of the first year of life was associated with later persistent wheezing and asthma<sup>12, 131</sup>.

#### 1.4.5.2 ELSPAC (1991)

The European Longitudinal Study of Pregnancy and Childhood (ELSPAC), initiated by the WHO office in Copenhagen in 1985, aims to identify factors influencing children's health in European countries<sup>127</sup>. Currently a total of 11 study centres are collecting data in six European countries<sup>127</sup>. Recruitment was limited to births over 18 months between 1991 and 1995, country dependent<sup>127</sup>. The primary research instruments are questionnaires for the child, their mother, father, siblings, teacher and a health status questionnaire<sup>127</sup>. The ELSPAC plans to collect data from at least one more phase and are supported to continue until the cohort are at least 21 years of age<sup>127</sup>. Hundreds of papers using original data have been published. An additional large-scale project is the Environmental Health Risks in European Birth Cohorts (ENRIECO) project (2009) that has been funded by the European Union<sup>135</sup>. This project aims coordinate birth cohort research in Europe in the area of environmental contaminant exposures<sup>135</sup>.

## 1.5 Conclusion

Respiratory symptoms in preschool children are difficult to assess using objective measures. This problem can be avoided by using indirect measures of lung function such as parental completed respiratory symptom questionnaires. Numerous respiratory questionnaires have been validated for adult and paediatric populations, however few have been validated for the preschool populations. The LRSQ is the most appropriate questionnaire for studying preschool respiratory symptoms, particularly in Liverpool, as it has been previously validated in this population. . In addition it enables the exploration of the burden of these symptoms upon children and their families in future respiratory studies. However, it has been accepted that this questionnaire requires further validation using a larger cohort. Birth cohort studies are an invaluable tool for epidemiological studies.



## 2 Protocol Development

### 2.1 Justification of the LRBCS

The LRBCS is the first proposed prospective birth cohort study to use the LRSQ. It will collect a range of information regarding respiratory symptoms of preschool children and other risk factors predisposing children to respiratory and related disease. This study enables exploration of the effect of demographics and exposures upon the respiratory health of the Liverpool paediatric population. Liverpool is a particular region of interest as it is considered to be one of the most socially deprived cities in the United Kingdom. This chapter will further describe the deprivation in Liverpool in addition to the respiratory health of the paediatric and adult population.

#### 2.1.1 Using the LRSQ

The LRSQ has proven itself as a valid, tool for assessing respiratory symptoms in preschool children, further validation is now required using a larger cohort of patients<sup>79, 80</sup>. A unique feature is that it provides a platform for exploring the impact respiratory symptoms have upon the quality of life of the child and their family. Having been developed by a team of Paediatricians at Alder Hey Children's Hospital NHS Foundation Trust, it offers an expertly designed tool that may be easily completed by parents.

### 2.1.2 Respiratory Disease in the United Kingdom

Respiratory disease incurs a significant and increasing burden upon the health resources of the UK, now costing the NHS an incredible £6.6 billion annually (2004)<sup>136</sup>. The relative burden of respiratory disease in the UK is unchanging, while the burden of ischaemic heart disease (IHD) is decreasing<sup>136</sup>. Respiratory disease is the third most commonly reported long-term illness in the UK<sup>136</sup>. Over 6% of men and women reported having a long-term respiratory illness<sup>136</sup>. Respiratory disease causes one in five deaths annually, these figures are greater than those for IHD<sup>136</sup>. Notably, social inequality causes a higher proportion of deaths in respiratory disease than any other disease area<sup>136</sup>. Approximately 44% of all deaths from respiratory disease are associated with social class inequalities, compared to 28% of deaths from IHD<sup>136</sup>. Furthermore, respiratory conditions are the most commonly reported long-term illnesses in children and babies<sup>136</sup>. Respiratory system disorders are the most commonly reported long-standing illness in both boys and girls in England<sup>136</sup>. Lung cancer is the second most common cancer in both men and women and survival rates for lung cancer are very low; the five-year survival rate for men and women is 6.3% and 7.5%, respectively<sup>136</sup>.

Not only does respiratory disease incur a significant burden upon the health of the UK population but these subsequent results in financial and social implications. Nearly 25 million certified sickness absence days were claimed for respiratory disease in 2002/03, not including days lost from self-certified illness<sup>136</sup>. Within the community, rates consultations for respiratory conditions are higher than any other illness, particularly for infants, young children and the elderly<sup>136</sup>. Respiratory symptoms are prevalent in about one fifth of the population<sup>136</sup>. Furthermore over a fifth of children had a diagnosis of asthma between the years of 2002 and 2003<sup>136</sup>.

### 2.1.3 Respiratory Disease in Liverpool

The health and well being of children in Liverpool is generally worse on average than in England<sup>105</sup>, particularly with regards to the English population<sup>137</sup>. Asthma prevalence is approximately 6% of the population while emergency admission for acute asthma in adults is as high as 98.04/100,000 of adults aged over 18<sup>137</sup>. The region also has among the highest emergency admission rates for chronic obstructive pulmonary disease (COPD) in England and high re-admission rates<sup>137</sup>. In addition to high mortality rate for those ages less than 75 years, COPD mortality is also very high being, 47 out of 100,000<sup>137</sup>. Liverpool has the highest incidence of emergency admissions rate for children with acute asthma in England (733 per 100,000 for children aged 0-17 years)<sup>137</sup>. Furthermore, Liverpool also has one of the highest average incidence of bronchiolitis, approximately 4,412 per 100,000 of children aged <2 in 2010-11<sup>137</sup>.

Historically, Liverpool is an established site for exploring respiratory symptoms and air pollution. Past studies from the Merseyside Respiratory Health Surveys (MRHS) (1991) identified that children living within 2km of the old dock area were almost twice as likely to experience cough and breathlessness than children living further away<sup>138</sup>. These results were not limited to those living within this region. Children attending primary schools within 2km of the docks were also been shown to have a 40% increase in excess cough and school absence due to respiratory problems<sup>138</sup>. This is compared with children in control schools located away from the exposed area<sup>138</sup>. In addition to respiratory symptoms, school absence is significantly associated with proximity to the Liverpool docks<sup>138</sup>.

Increased prevalence of respiratory symptoms and doctor diagnosed asthma (DDA) were shown to correspond to proximity to the source of dust pollution levels and distance from the docks<sup>138</sup>. Results confirm previous hypotheses, that the increased respiratory symptoms in children in North Liverpool have been exacerbated by dust pollution<sup>138</sup>. It was also concluded that children exposed to dust pollution were at higher risk of respiratory morbidity<sup>138</sup>.

However, authors noted that caution must be taken in observational studies when attributing cause and effect in the absence of adjustments for known confounding factors including family history of asthma, parental smoking, and socioeconomic factors<sup>138</sup>. Since this data was collected, the dock area in Liverpool has changed considerably. The majority of the docks are dormant particularly within the Bootle area, while some active docks remain in the Seaforth area.

Established in 1991, the MRHS consists of three cross-sectional respiratory health surveys were completed in 1991, 1993, 1998 amongst children aged between 5 to 11 years<sup>139</sup>. Results showed a significant increase in DDA, by 12.1%, between 1991 and 1998 in Mersey primary school children<sup>139</sup>. In these studies socioeconomic deprivations, assessed using the Townsend index, were independently associated with DDA and the respiratory symptoms; cough, wheezing and breathlessness<sup>139</sup>. The rising prevalence of these DDA has also been reported in previous studies<sup>133</sup>. Higher respiratory symptoms may result from more deprived populations being less prone to seek or comply with health care<sup>139</sup>. Furthermore, women from poorer socioeconomic backgrounds are more likely to deliver pre-term babies<sup>139</sup>. Preterm birth has been shown to predispose the child to subsequent development of asthma<sup>140</sup>. Premature babies of asthmatic mothers are also at very high risk of childhood symptoms and asthmatic mothers are more likely to have preterm deliveries<sup>140</sup>.

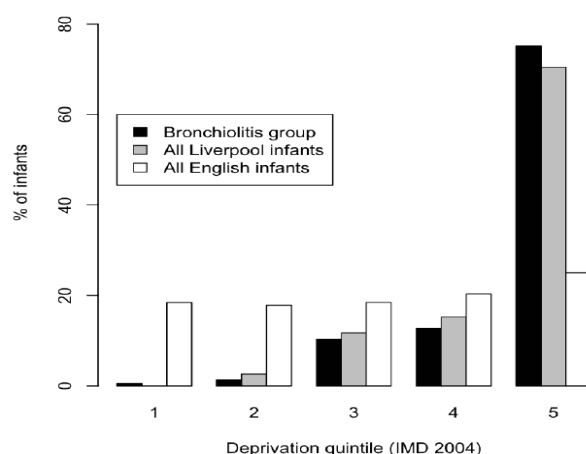
Between 1998 and 2006 a further four, standardized cross-sectional school surveys, were undertaken to collect additional data for the MRHS<sup>141</sup>. Analysis from these more recent surveys showed a significant decrease in the prevalence of parentally reported doctor diagnosed asthma (DDA), wheezing and allergy among Merseyside primary school children<sup>141</sup>. This may be as a result of a change in the Liverpool dock area since the initial surveys between 1991 and 1998. The decrease in early childhood wheezing contrasts with parental asthma prevalence, that increased over the same period<sup>141</sup>. However, decreasing parental response rates may have led to biased data over the years<sup>141</sup>.

Poorer birth outcomes reported in the 2006 survey might be expected to lead to increased and not reduced asthma risk, as preterm birth was significantly related to DDA in the regression analysis<sup>141</sup>. This decrease in DDA is reportedly consisted with other studies and may related to changing patterns of respiratory infections in children with reduced environmental exposures<sup>141</sup>. Variability in the diagnosis of asthma must also be considered, as it is a subjective measure. A study by Kelly et al concluded that the symptom triad of cough, wheeze and breathlessness might be a more reliable marker of true asthma in epidemiological surveys, rather than relying on either single symptoms or doctor diagnostic patterns<sup>140</sup>.

The Liverpool population has also been a used to evaluate the link between tobacco smoke and respiratory symptoms particularly as areas of social deprivation are reported to have a higher smoking population<sup>98, 142</sup>. Semple et al found that deprivation scores were significantly higher for households where a member smoked tobacco compared to non-smoking households and using a logistic regression model showed that deprivation predicts risk of tobacco smoking<sup>2</sup>. The study also showed that household exposure to tobacco smoke was a strong independent predictor of severe bronchiolitis<sup>2</sup>.

In another Liverpool-based study, Cooke et al found a clear relationship between parental smoking and the prevalence of asthma and respiratory symptoms in school children<sup>143</sup>. Semple et al were not only able to show that infants with bronchiolitis were more likely to come from deprived areas but in addition, that Liverpool was significantly more deprived, than the English population as a whole, using the Indices of Multiple Deprivations (see figure 2.1)<sup>2</sup>.

**Figure 2.1: Deprivation in Liverpool by Semple et al<sup>2</sup>**



### 2.1.4 Deprivation in Liverpool

Deprivation has a longstanding link to health but is multidimensional and therefore challenging to quantify<sup>144</sup>. In the UK, each of the four constituents uses their own distinct indices of multiple deprivations (IMD) to measure deprivation<sup>144</sup>. The results of which facilitate the development of policies targeting issues within that particular country<sup>144</sup>. There are however, many measures of deprivation in common use. These include the Townsend Material Deprivation Score or Townsend Index, Carstairs Index, Jarman score DETR 2000 and more recently the Index of Multiple Deprivations (IMD) designed in 2000<sup>145</sup>. The Townsend Index and the Carstairs Index are similar measures that were both developed as measures of material deprivation<sup>145</sup>. Both the Townsend Index and the IMD have been used in numerous studies as a measure of disadvantage and deprivation, subsequently giving an overview of inequalities<sup>144</sup>. The more recent IMD includes measures of income, employment, health, disability, education, housing, environment and crime<sup>144</sup>.

Liverpool has a longstanding history of being of much poorer health than most of the country. There are persistently high levels of deprivation in the city and figures from 2010 show that Liverpool remains ranked as the most deprived local authority area in England, a position unchanged from the 2004 and 2007 Indices<sup>146</sup>. Significant inequalities remain between Liverpool and the rest of the country. This compares to Manchester and Knowsley ranked at four and five respectively, in the Northwest<sup>147</sup>. The Health Deprivation and Disability domain contains the highest levels of deprivation, with 17.5% of Liverpool's Lower Layer Super Output Area (LSOAs) in the most deprived one per cent nationally and 61.9% of LSOAs in the most deprived ten per cent<sup>146</sup>. The average life expectancy is also poor compared that other regions in England and Wales<sup>148</sup>. Women have the second worst life expectancy in England and Wales at 79.2 years and are expected to die 3.4 years younger than the national average of 82.6 years<sup>148</sup>. While men have the 5th worst life expectancy in England and Wales at 74.8 years (2008-2010), and are expected to die 3.8 years younger than the national average of 78.6 years<sup>148</sup>.

Infant deaths can also be an important indicator of inequality and children. Between 2008-2010, Liverpool had a rate of 4.9 deaths per 1,000 live births, however this is not significantly different from the England average of 4.4 per 1,000<sup>148, 149</sup>. Liverpool does however, have some of the highest levels of child poverty in the UK. One in three children in Liverpool (34%) live in poverty, compared to one in five children in England (20.9%) this equated to over 30,000 children<sup>148</sup>. Health inequalities in childhood lead to health inequalities in adulthood, which only highlights the importance in reducing these inequalities as early on as possible<sup>148</sup>. Children are said to live in poverty when they live in families, which lack the resources to enable their children to participate effectively in ordinary patterns of living, meaning they may be excluded from many aspects of everyday life<sup>148</sup>. Life expectancy at birth for Liverpool boys and girls are profoundly different when compared with the English average (79.2 compared with 78.6 and 82.6, respectively). Subsequently Liverpool provides a platform for assessing respiratory symptoms in areas of profound deprivation.

### **2.1.5 Describing and quantifying the impact of respiratory disease**

The impact of respiratory disease and symptoms upon the infant's family is important to quantify because it provides an insight into the burden of respiratory disease within society. It also allows research to establish which areas need to be prioritised in terms of support and future policy development. In addition, predicting the need for childhood respiratory care by measuring onset and severity of respiratory symptoms and their access to care. These results in combination with results relating to the natural history of respiratory symptoms provides evidence and guidance into the future development of health promotion initiatives and social policies for the city of Liverpool. With better information, the department of health, local health boards and may develop public health interventions and policies developed specific to the needs of the Liverpool population or even nationally.

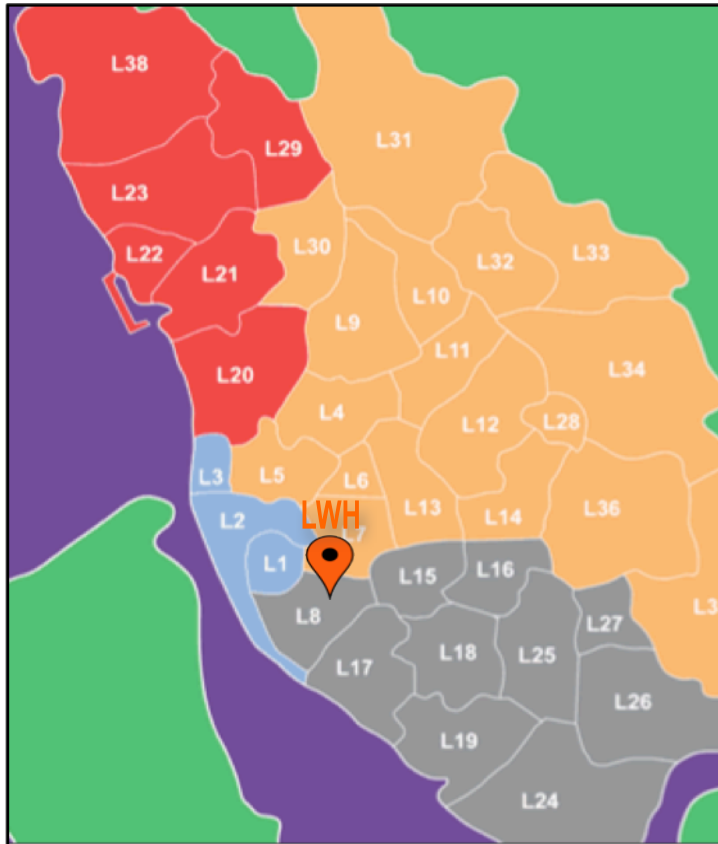
Identifying the burden of respiratory disease also makes the case for further and more urgent action to prevent and control respiratory diseases and factors that may cause respiratory symptoms or disease. The impact of disease is often under recognised and underestimated, particularly with regards to respiratory disease. Respiratory disease has a negative impact on not only the health but upon the wellbeing of families<sup>150</sup>. Identifying the impact of disease offers clinicians an insight into the affects of respiratory disease and symptoms upon family relationships and treatment decisions<sup>150</sup>. Birth cohort studies are able to identify risk factors and incidence of disease and subsequently identify ways in which to prevent disease. Overall the population of Liverpool in particular will benefit, as this information will aid planning, development and the implementation of social policies and strategies. The health board and support services may also benefit, as it will provide a case for better allocation of resources and provide more efficient and effective services.

#### **2.1.6 Recruitment at the Liverpool Women's Hospital**

The Liverpool Women's Hospital (LWH) is the sole provider of maternity services for the Liverpool Primary Care Trust (PCT) and more recently the Liverpool Clinical Commission Group (CCG). Its central location (see figure 2.2) makes it accessible to the majority of women living in Liverpool. The LWH claims to be the largest single site maternity hospital in Europe and has an estimated 8,400 infants born annually. The hospital provides access to the majority of eligible babies and an invaluable opportunity to base recruitment at a single site. In addition, contacts at the LWH facilitate the development of a feasible recruitment strategy. Experienced paediatricians and senior midwives facilitated the development of a site-specific recruitment plan.



**Figure 2.2: Map showing location of LWH within the Liverpool Postcodes**



However, St Helens and Knowsley NHS Trust and Southport and Ormskirk NHS Trust also offer maternity services at both Whiston and Ormskirk Hospitals. This must be considered when analysing results, particularly as recruitment will be sparse within these trust's catchment areas.

## 2.2 Method Development

The protocol was developed following the recognition of the LRSQ as a valuable tool for assessing respiratory symptoms. The authors of this tool kindly gave permission for its use and provided the opportunity for the first respiratory birth cohort study using the LRSQ to begin development.

Important initial factors to consider during the design of this protocol were;

1. Which demographic and exposure data to collect
2. Recruitment and follow up strategy
3. Questionnaire design and deployment

### 2.2.1 Demographic and Exposure Data

One of the important factors to consider was which demographic and exposure data needed to be collected from participants. Initial ideas suggested were date of birth, age, sex, prematurity, birth weight, bronchiolitis, smoking and breastfeeding. Previous cohort studies have reported these variables (see table 2.1)<sup>110, 113, 114, 151</sup>. Risk factors noted from literature are summarised in the table below. The final categories for data collection were finalised following discussion with senior paediatricians Dr Calum Semple and Professor Ben Shaw, and after reviewing past birth cohort studies and respiratory studies in children<sup>110, 114, 151</sup> (see protocol in text below).

**Table 2.1: Risk factors for respiratory symptoms in paediatrics**

Exposures	Demographics
Cigarette smoking <sup>152, 153</sup>	Prematurity <sup>154, 155</sup>
Air pollution <sup>156, 157</sup>	Low birth weight <sup>158, 159</sup>
Social deprivation <sup>160, 161</sup>	Male gender <sup>162, 163</sup>
Overcrowding <sup>164, 165</sup>	Co-morbidities <sup>166, 167</sup>
Breastfeeding <sup>168, 169</sup>	
Exposure to other children <sup>170</sup>	

### 2.2.2 Consent, Recruitment and Retention Strategies

The recruitment strategy needed careful planning, involving discussion with senior paediatricians in addition to reviewing current literature. Initially recruitment was intended to tie in with baby checks performed by the paediatricians. After reviewing literature on recruitment for birth cohort studies and much discussion it was decided that mothers would be personally recruited by dedicated research staff. A great deal of evidence proves that personal recruitment is the most effective strategy<sup>110, 151, 171, 172</sup>. With recruitment designated to one particular person it maintains consistency not only with regards to data but also with staff at the LWH. Recruitment involves a two-stage process. The first stage involves mothers' expression of interest once approached at the LWH. The second involves consent to take part in the study, which takes place 4 months after birth when new mothers receive the initial questionnaire.

### 2.2.3 Questionnaire Deployment

Questionnaire deployment will primarily take place by means of email, as it is the most cost effective and efficient method of deployment. In addition, questionnaires deployed may be completed quicker and be modified easily throughout the study. The questionnaire will be primarily completed online, accessed by clicking a unique link sent in the email. However an additional postal option was retained as without this, patients without access to web enabled technology would be unable to take part. The most reasonable frequency for questionnaire delivery was deemed to be six monthly, particularly as the questionnaire reviews symptoms over the last three months. Researchers also reasoned that this should not burden parents extensively. The questionnaire will be sent out at particular ages i.e. four months from birth then six months subsequently preventing seasonal bias, if the questionnaires were sent in batches at specific time-points.

Finally, Professor Shaw kindly gave permission for the front and last page of the original questionnaire to be edited for the web-based questionnaire. The original front page consisted of questions regarding contact details and demographic details and these were simply re-ordered following Patient and Public Involvement (PPI) at the LWH. The final section will gather information about treatment and interactions with health care services; the exclusion of this section does not affect the validity of the symptom component of the questionnaire. These questions again were edited during the design of the web-based questionnaire following PPI work at the LWH.

## **2.3 Revisions to Protocol**

Three consultant paediatricians reviewed the initial draft of the protocol. These were Dr Calum Semple, Professor Ben Shaw and Dr Kevin Southern. The study outline was also presented at the Liverpool Research Forum at Alder Hey Children's Hospital where valuable feedback was given by clinicians and researchers regarding the study methodology and design. Revisions have also been made since the addition of another MPhil student to the team after additional survey and email software was explored (table 2.2). Patient involvement was also a very important factor to help determine survey software, questionnaire format, design and layout and method of deployment.

**Table 2.2: Summary of Protocol Revisions**

<b>Revisions</b>	<b>Summary</b>	<b>Reason</b>
Recruitment method	Personal recruitment by study staff as opposed to NHS staff or study advertisement.	Evidence and personal experience of senior researchers deemed this the most suitable and potentially effective method.
Survey software	Survey software was changed from Select survey to Adobe forms central.	Select survey was initially recommended by the university due to its ease of use and collaboration with university surveys. However after exploring the extensive features of adobe survey software and feasibility testing using mothers, adobe forms central was shown to be the best choice. This is described further in chapter 5.
Start date for recruitment	Date for initiating recruitment was pushed back	This was necessary due to unforeseen circumstances, administration and feasibility testing

Below is the complete, finalised version of the LRBCS study protocol. The text of the protocol is outlined in a text box to discriminate it from the body text of the thesis.

## 2.4 The Protocol

**The Liverpool Respiratory Birth Cohort Study: A Prospective, Longitudinal Birth Cohort study using the Liverpool Respiratory Symptom Questionnaire to conduct a biannual assessment of the respiratory symptoms of preschool children born in Liverpool from birth until the age of five years.**

### Abstract

**Objective:** To describe respiratory symptoms of preschool children using the Liverpool Respiratory Symptom Questionnaire (LRSQ) from birth until the age of five years, in Liverpool by bi-annual assessment.

**Method:** Newborn infants will be recruited during their mother's stay at the Liverpool Women's Hospital (LWH). Prior to discharge, research students will provide information to mothers about the study in the form of a postcard. Mothers will be asked to fill in their contact details including email and phone number indicating their interest in taking part. Completion of the postcard implies consent to be contacted. Postcards may be deposited in collection boxes at the LWH. Once the research team have received the postcards, parents will later be sent an email or letter thanking for their interest in the study. When the baby is four months old an email will be sent to the mother, which will include an option to consent to take part and a link to the initial online questionnaire. Mothers may alternatively opt to receive the questionnaires by post. The questionnaire will then be emailed or posted to mothers six monthly until their child is five years old. Demographic details will be requested on initial enrolment and confirmed or updated during the course of the study. Data will be hosted on-line by Adobe Forms Central software in an encrypted and anonymised format and stored on secure servers at the University of Liverpool.

**Analysis:** Demographic, exposure and LRSQ data collected by Adobe Forms Central software, which is compatible with the statistical analysis software SPSS™. Univariate and multivariate analyses using linear regression analysis will be used to compare domain scores of the LRSQ scores with exposures/variables such as prematurity, birth weight, deprivation and exposure to cigarette smoke in pregnancy and in the household. Structural equation analysis and multinomial regression analysis will also be used to assess any relationship between exposure/demographic variables and respiratory symptoms. Cronbach's alpha coefficients will be calculated to assess internal validity.

## Introduction

A literature search of birth cohort studies that explore respiratory symptoms revealed 129 studies conducted between 1961 and 2011 written in the English language. Of these 129 studies 17 separate respiratory birth cohort studies were identified. Among the UK studies identified are the AVON study using the Bristol cohort, the 'Children of the 1950's and the National Child development study. International studies specifically focusing on respiratory symptoms include the Tucson Cohort and the ISAAC study. All use a respiratory questionnaire to assess respiratory symptoms, but none assessed the impact of respiratory symptoms on both preschool children and their parents. The Liverpool Symptom Questionnaire (LRSQ) is specifically designed to assess the impact of respiratory symptoms on preschool children and their parents. This study is the first proposed birth cohort study to use the LRSQ.

Over the last few decades numerous questionnaires have been designed to explore the respiratory symptoms of adults and children. Many studies have since been conducted to examine the validity of these questionnaires. Questionnaires may be delivered by an interviewer, be completed by either the patient themselves or by the parent's of the patient. Self-completion questionnaires have proven to be more economical and also help reduce observer bias when compared to interview questions <sup>173</sup>.

A literature search was conducted using Medline. Keywords searched include 'respiratory' 'symptom' and 'questionnaire'. The results were limited to the dates 1991 to 2011. In total 775 articles were identified and reduced to 69 after reviewing titles and abstracts to determine relevance. The 69 articles related to 36 different respiratory symptom questionnaires for both children and adults and enabled identification of the most commonly used questionnaires.

Questionnaires for respiratory symptoms commonly used in adults include the St George Respiratory Questionnaire (SQRQ), the American Thoracic Society Standardized Respiratory Questionnaire (ATSq), the Global Allergy and Asthma European Network Questionnaire (GA2LENq) and the MRC respiratory symptom questionnaire. The most commonly used questionnaires in the studies identified are the SQRQ and modified versions of the ATSq. The primary symptoms explored using the questionnaires are cough, wheeze, and breathlessness. Many studies have edited existing questionnaires to include questions on smoking, occupational hazard and various other exposure or occupational respiratory hazards. The most commonly used questionnaire's available specifically for children include the ISAAC questionnaire for ages 6 years to 13 years, and the Test for Respiratory and Asthma Control in Kids (TRACK). Both questionnaires have been validated by numerous studies. Many of the adult questionnaires explore the impact of respiratory symptoms upon the patient. The St Georges Questionnaire for adults addresses the affect of respiratory symptoms upon patient but not upon the family. The Wisconsin Upper Respiratory Symptom Survey (WURSS 44) includes questions on whether the persons cold has affected their daily activities, work inside and outside their home, interact with others and personal life <sup>42</sup>. The Living with Asthma Questionnaire explores the impact of asthma on the person completing the questionnaire, however this is a questionnaire designed for adults and is specific to Asthma and doesn't necessarily incorporate any other respiratory condition <sup>174</sup>.



As discussed many adult questionnaires explore the impact of respiratory symptoms upon the patient and their lives. However, currently no preschool questionnaire for parental completion explores the impact of these respiratory symptoms on the children and their parents. There are also very few respiratory questionnaires validated specifically for the preschool age groups and the LRSQ addresses both these issues.

The LRSQ is a validated tool that explores the prevalence of respiratory symptoms in infants and preschool children. This parental completion questionnaire was first designed using established criteria, as a follow up tool for use in neonatal studies where the outcome of children two to three years of age was of interest. A unique feature of the LRSQ is that it also explores the impact of wheeze attacks and other respiratory symptoms upon the child and their family. The LRSQ consists of nine domains. Each domain contains between three and five questions seeking responses scored on a five point Likert scale from “not at all” (score 0) to “every day” (score 4) The first six domains assess respiratory symptoms such as wheeze and cough. The next two assess the effect on the child and their family. The final section asks for details regarding medication, GP/clinic visits, hospital admissions and labels given. All domains ask parents to consider symptoms/effect over the last three months.

Birth Cohort studies are an invaluable tool for studying the epidemiology of specific populations. This study aims to map the natural history of respiratory symptoms of preschool children born in the Liverpool. It is likely to be an invaluable tool to assess the complex relationships between childhood respiratory symptoms and deprivation, premature birth, birth weight, smoking in pregnancy and smoking by household members. Liverpool is recognised as being of the most deprived cities in the England with high rates of cigarette smoking <sup>175</sup>. This permits for reliable studies into these effects and makes Liverpool an ideal location for a birth cohort study. The majority of births occur at one centre facilitating recruitment.

### **Work underpinning this study**

Three studies have been conducted using the LRSQ. The first, by Powell et al (2002) developed and validated the standardised questionnaire <sup>79</sup>. After reviewing other questionnaires we find that most do not explore the impact of specific respiratory symptoms, including wheeze, on the child and their family. However, the LRSQ does this well with two of nine domains exploring the impact of respiratory symptoms on both the child and their family. A relatively small cohort was used for initial exploration of the questionnaire, however the authors justify this as a reasonable number, as other questionnaire used similar figures. After assessing particular areas such as response rates and reliability, the authors demonstrated that it is an acceptable questionnaire, easily completed, with good response rates <sup>79</sup>. However they did not attempt to examine the readability in detail or looked at factors, which may affect responses <sup>79</sup>.

The second was a cross sectional study that explores respiratory symptoms in Cystic Fibrosis <sup>80</sup>. This study also further validated the questionnaire's external and internal validity. The study showed that the LRSQ has good internal validity across 6/8 domains. It covered an extensive number of symptoms while also maintaining acceptability. It also demonstrated the LRSQ as a potential tool for assessing and monitoring respiratory symptoms in preschool children with cystic fibrosis.

A small, unpublished cross-sectional study has also been conducted using the Liverpool cohort, which used the LRSQ to explore respiratory symptoms in infants following exposure to RSV bronchiolitis. This study again demonstrated good internal validity using the Cronbach's coefficient but also enabled identification on small issues with the design of the questionnaire with the possibility of many improvements that may help with data collection and improve the clarity of the questionnaire.

## **Justification of this study**

A literature search was conducted identifying birth cohort studies that feature a respiratory component. Among the UK birth cohort studies identified were the AVON study a large longitudinal birth cohort, which recruited over 14,000 pregnant mothers from the Bristol Cohort <sup>112</sup>. The 'Children of the 1950's' is a large study conducted on the Aberdeen cohort followed children born in the 1950's up until adult life. The British National Child Development Study (NCDS) started in 1958 and recruited all births within one week in the UK. International studies specifically focusing on respiratory symptoms include the Tuscon Cohort and the International Study of Asthma and Allergy in Children (ISAAC) study. Both of these use a respiratory questionnaire to assess respiratory symptoms, but did not apply it in preschool children.

The LRSQ has demonstrated potential as a tool for assessing respiratory symptoms in preschool children. The validity and utility of the LRSQ have been assessed in two previous studies, demonstrating it to be a useful tool for assessing respiratory symptoms in preschool children however further validation is required, using a larger cohort of patients. Many large birth cohort studies have been conducted in the UK and Internationally.

This is the first proposed prospective birth cohort study to use the Liverpool Respiratory Symptom Questionnaire. This study will enable a large range of information regarding respiratory symptoms of preschool children and other risk factors predisposing children to respiratory and related disease. It enables numerous future studies to be conducted using the data collected. It allows exploration of respiratory symptoms in relation to demographic details and details of exposure to risk factors which is particularly of interest in Liverpool, as it is considered to be one of the most socially deprived cities in the United Kingdom<sup>175</sup>.

## **Research Method**

### **Study design**

This is a longitudinal birth cohort study using the parent completed Liverpool Respiratory Symptom Questionnaire (LRSQ) to assess preschool children's

respiratory symptoms from birth up until the age of five years old. This study will also provide the opportunity for additional cross-sectional studies to be conducted on the patient group recruited and the results gathered. It is important to note that there will be no specific interventions made by the study.

**Setting:** Children normally resident in Liverpool postcodes L1-38.

### **Recruitment**

We propose a maximum recruitment strategy and aim to recruit as many infants born at the Liverpool Women's Hospital as possible from January 2013. Recruitment will be limited only to parents domiciled within the Liverpool postcodes L1-38.

Newborn infants will be recruited during their mothers stay prior to discharge from the Liverpool Women's Hospital. Research students will personally provide information to mothers about the study verbally and in the form of a postcard while the mothers are at the Liverpool Women's Hospital. Mothers will be asked to fill in their contact details including email and phone number indicating their interest in taking part. Completion of the postcard implies consent to be contacted. Mother's hospital stickers will also be attached to the postcard. In addition, the postcard will also include a QR(2D) bar code which mothers may scan using their smart phones. This QR code will direct participants immediately to an online version sign up version of the postcard.

Once completed, research students will collect the postcards. Alternatively mothers, midwives or volunteers at the Liverpool Women's Hospital may deposit the postcards in a collection box. Once the research team have received the postcards contact details will be uploaded to the database sorted on the University of Liverpool's secure server. Within a week, parents will be sent an email thanking for their interest in the study. The next point of contact will be when the baby is four months old. An email will be sent to the mother, which will include a link to the initial online questionnaire. This email will include; information about the study, consent, questions regarding demographic and exposure details and the LRSQ in a series of separate but easily understandable pages. Mothers may alternatively opt to receive the

postal questionnaires, which will be first sent within a week of the baby being four months old.

Recruitment material will make no therapeutic promises, as this is only a descriptive study. The inclusion and exclusion criterion ensures that no one is unfairly excluded from the study. All data collected will be automatically deposited on a password database on a secure server in the University of Liverpool. Where parents have indicated that they would prefer hard copy (paper) correspondence, this will be sent with a stamped address envelope for return. The research student will enter this data by hand. Data will be imported into an SPSS database on a case-by-case basis.

### **Follow Up**

Consent will be obtained when the initial questionnaire is sent, four months after birth. Following that, a second email will be sent six months later and every six months thereafter until the child is five years old. This repeat mailing questionnaire will provide an option for participants to update any contact details and will include demographic and exposure questions and the LRSQ questions.

In addition, on the date of their child's birthday, mothers will receive a personalised email thanking them for taking part in the study and wishing their child a happy birthday. In the case of no reply, two reminder emails will be sent and if no response this will be followed by one contact by telephone and one postal contact as email addresses and telephone numbers may have changed over time. Each contact attempt will be two weeks after previous attempts. For mothers without email addresses or access to computers, reminders will be made by telephone and mailed by post.

With each email sent, mothers will be given an option to sign up to updates regarding recruitment and reports on any preliminary findings. Families who move out of the area will be asked to continue their involvement. Contact will continue by email and telephone. The questionnaire will include an option to update place of residence among other details.

### **Data Collection**

Data will be linked from the on-line Adobe Forms Central Survey software into a SPSS database on a case-by-case basis throughout the duration of the study. The data collected from postal questionnaires will be inputted into the online survey manually by and subsequently inputted into the database by the research student.

### **Inclusion criteria**

All infants born at the Liverpool Women's hospital, including premature births, where parents are normally resident in Liverpool postcodes (L1-38) regardless of future residence.

### **Exclusion criteria**

Neonates born to parents normally resident outside the Liverpool postcodes L1-38.

Babies born to non-English speaking parents.

Babies taken into the care of local authorities.

## **Variables and Outcomes Measures**

### **Aim**

To establish a population based longitudinal birth cohort study conducting a bi-annual assessment of respiratory symptoms of preschool children using the LRSQ from birth to the age of five in Liverpool.

**Primary objective:** To describe parent reported respiratory symptoms in a population based birth cohort followed longitudinally from birth to five years old using the LRSQ.

**Secondary objectives:** To examine any association between differences in respiratory symptoms in groups of preschool children with different social and environmental risk and protective factors.

## Bias

To minimise withdrawals from the study patients will be given three reminders, two via email and one by telephone contact after initial email of the questionnaire. Recall bias is not considered to be a problem, as the questionnaire requires parents to report respiratory symptoms in the last three months and this recall period has been validated for this questionnaire. In the three previous studies parents have not fully completed the questionnaire, which may introduce reporting bias. Using the online questionnaire may help, as software prompts parents to complete all questions and can give options for null responses rather than leaving 'blanks' on paper.

## Demographics and Exposure Variables

### Figure 2.3 Demographics

- Sex of child
- Age of child
- Date of Birth
- Postcode
- Ethnicity of child
- Gestation at birth
- Birth Weight (kg or lb/oz)
- Mother's highest qualification
- Breastfeeding duration (weeks/months)

### Figure 2.4 Exposure variables

- Nursery Attendance
- Persons sharing the child's bedroom
- Number of siblings living in a household
- Maternal smoking during pregnancy (any)
- Smoking by any household member in the last 3 months regardless of location
- Chronic co-morbidities
- Family history of atopy

## **Proposed Study Size**

We plan a maximum recruitment strategy from the Liverpool Women's Hospital where there are approximately 8,000 births each year. We estimate that approximately one in four mothers will complete the postcard provided. The questionnaire currently has a 13% return rate therefore we expect approximately 260 patients to participate in the study each year. Comparison of demographic data for those participating with census data will allow a check for recruitment bias.

## **Statistical Methods**

The results from questionnaires on Adobe Forms Central will be uploaded to SPSS and analysed using the SPSS Statistical software. Rolling cumulative data analysis will be performed for the duration of five years.

Univariate and multivariate analyses using linear regression analysis will be used to compare domain scores of the LRSQ scores with exposures such as maternal smoking etc. Fishers exact test will be used to determine whether there is any relation between two categorical variables. Structural equation analysis and multinomial regression analysis will also be used to assess any relationship between exposure/demographic variables and respiratory symptoms. Cronbach's alpha coefficients will be calculated to re-assess internal validity. In this study missing data is most likely to result from failure to respond.

## **Data Sources: Patient Demographic Service**

Data will also be collected from linked hospital episode data.

## **Data management**

Data will be collected from questionnaire answers via the Adobe Forms Central Software and linked directly to the programme SPSS for analysis.



## **Consent**

Mothers providing their contact details on the study information postcard implies consent to be contacted. The consent of mothers of patients will be sought when the first questionnaire is emailed or posted to participants. Mothers who are willing to participate will click on the embedded link to the questionnaire will be directed to a screen detailing more information about the study. After reading this they will be given the option to either not to participate and unsubscribe to emails, to contact the research team with any queries or to consent by clicking a button online and inserting their initials. After consenting to take part, mothers will be directed to the questionnaire. Mothers who opted for the postal questionnaire will be asked to complete a consent form alongside the initial questionnaire.

Patients and parents of patients at participating practices have the opportunity to opt out of the scheme at registration and any point thereafter by either contacting the research team or clicking a button on the email sent containing the LRSQ. [In studies involving postal questionnaires where the burdens are insignificant and sensitive topics are not involved, the REC will normal regard the return of the questionnaire as adequate evidence of consent (IRAS guidance 2012)].

## **Ethical Issues**

This study received REC ethical approval by proportionate review on 08/05/2012. (*REC Reference: 12/EM/0194*)

This study also received REC approval of minor amendments on the 08/11/2012.

This allowed use of the QR barcode on the postcard for recruitment and the use of a poster with the QR code for recruitment and advertisement of the study at the Liverpool Women's Hospital. No physical intervention will take place.

### **Data protection and Confidentiality**

The LRSQ database will include a unique study ID but no direct identifiers. The study ID and contact details will be kept in an encrypted data file in a secure server hosted by the University of Liverpool. Recruitment postcards will be archived securely at the Institute of Child Health, University of Liverpool. The questionnaire has only been validated in an English Language format. There is no capacity in this student project to develop and validate the LRSQ in other languages.

### **Risks to Patient**

There are few anticipated risks for research participants in this study. Possible risks include a breach in confidentiality with regards to contact details of patients and any personal data. Precautions will be taken to minimize the risk of this data will be stored very carefully. No identifiable data will be included in publications. Security data measures that will be taken include encrypting data with passwords, coding medical conditions and limiting access to study data.

An additional foreseeable risk identified is the risk of sending emails and questionnaires to parents of deceased children. Measures that could be taken include linking to the National mortality database via the Patient Demographic Service (PDS). The Alder Hey Children's NHS Foundation Trust's IT department will perform weekly batch searches linking to SPINE via the Patient Demographic Service. This, however, is not a foolproof method as there will be delays between the PDS being notified by the community and by Alder Hey Children's Hospital.

### **Benefits to patients**

There are no direct benefits to research participants taking part in this study. However there we hope that this study will benefit future preschool children by enabling us to identify risk factors associated with particular respiratory symptoms.

**Risks / benefits to study**

If too few participants are recruited this would compromise the results of the study. There is also the risk of losing patients to long-term follow-up. If patients are lost the data will still be included in the results.

**Research governance**

The University of Liverpool will be lead sponsor and the Liverpool Women's NHS Foundation Trust will co-sponsor for the study.

The proposed study will be undertaken in accordance with the University of Liverpool's research governance procedures.

Dr MG Semple (Liverpool University), Professor Ben Shaw (Liverpool Women's) will be joint guarantors for analysis and reports.

**The Research Team**

Miss Rosanna Pickles

Miss Bethan Griffiths

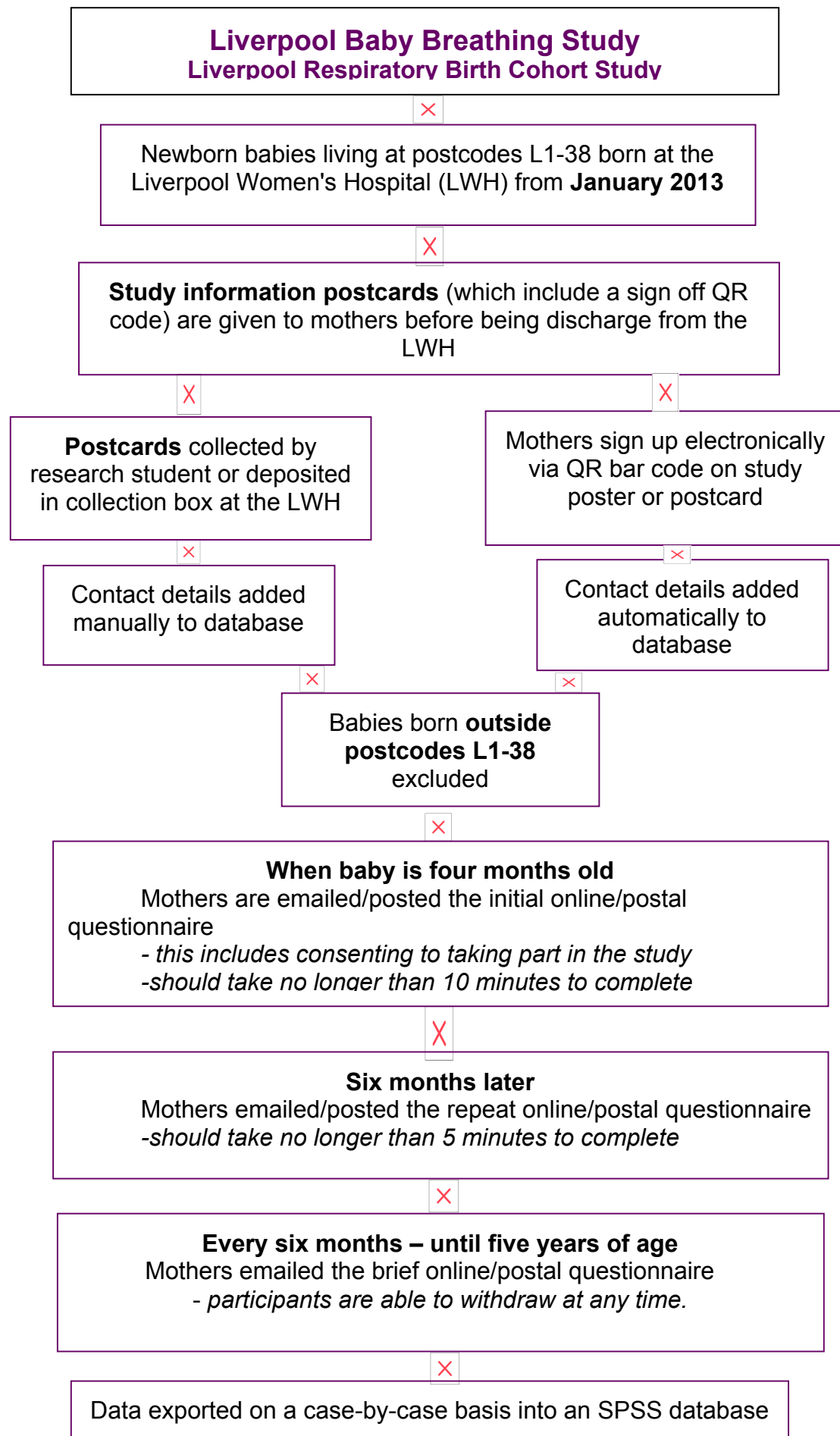
Dr MG Semple (Chief Investigator)

Professor Ben Shaw

Dr Kevin Southern

Dr Paul McNamara

Figure 2.5: LRBCS Study Method



## Timetable and Milestones

**Phase one** – Development of the protocol and supplementary document began in September 2011. The final protocol was used for ethics application via IRAS in April 2012. NRES approval was granted in May 2012.

**Phase two** – Development of the online questionnaire and consent form. Prior to the start of the study mothers will be interviewed regarding questionnaire aesthetics. Once the questionnaire design has been finalised the questionnaire will then be trialed at the Liverpool Women's hospital. Mothers will be interviewed while they are completing the questionnaire about the design, layout, format and content of questions; ease of use and asked to score the questionnaire out of ten. Mothers will also be asked about anything that would motivate them to participate in the study, and encourage continued participation.

**Phase three** – Recruitment of mothers and implementation of the study will begin on the 7<sup>th</sup> January 2013 and continue for a maximum of five years depending on the success of the study. The study will continue for a further five years after recruitment is complete.

### Expertise

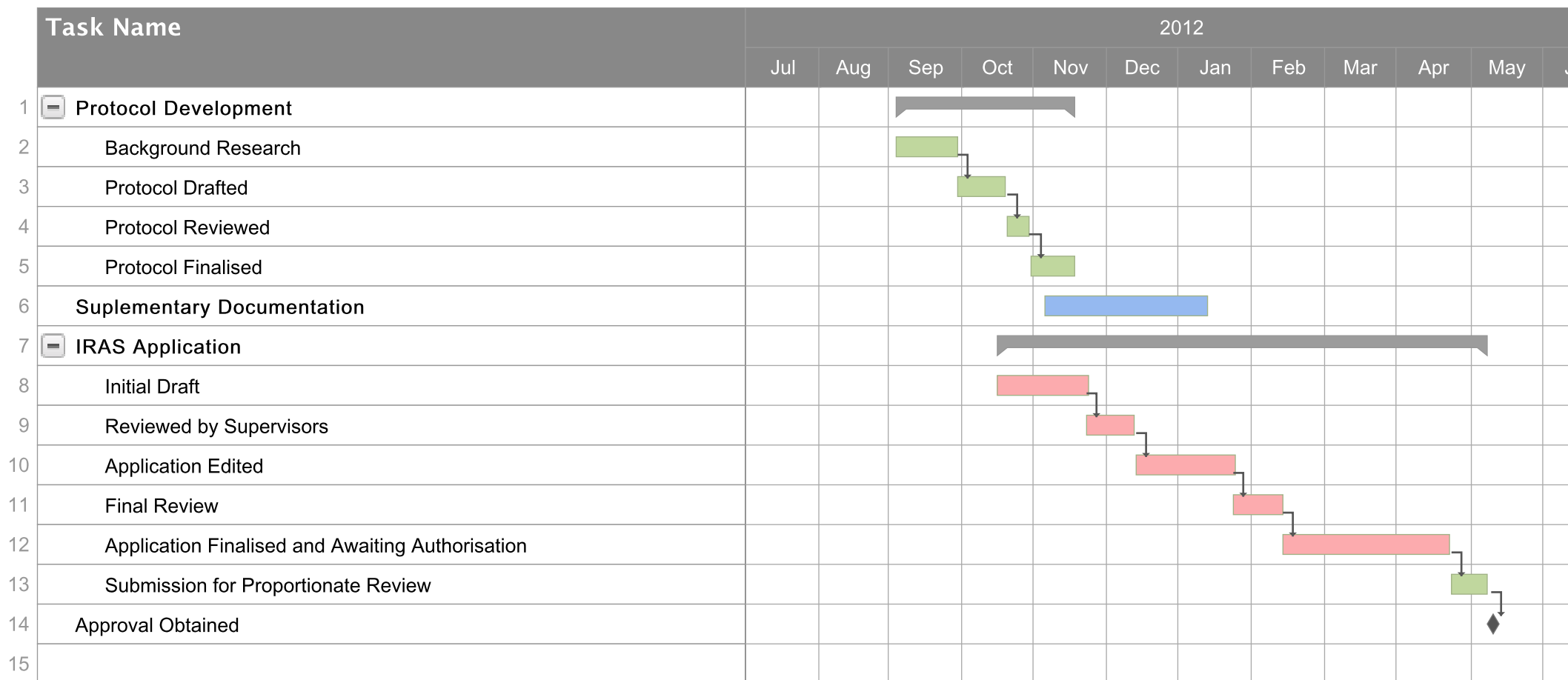
- Dr MG (Calum) Semple is a Senior Lecturer in Child Health at the University of Liverpool and Consultant in Paediatric Respiratory Medicine at Alder Hey Children's Hospital.
- Professor B Shaw, Consultant in Neonatal and Respiratory paediatrics at Liverpool Women's Hospital and the Royal Liverpool Children's Hospital.
- Dr Paul McNamara, Senior Lecturer in Child Health at the University of Liverpool and Consultant in Paediatric Respiratory Medicine at Alder Hey Children's Hospital
- Dr K Southern Reader in Paediatric Respiratory Medicine at the University of Liverpool and Consultant in Paediatric Respiratory Medicine at Alder Hey Children's Hospital

## **Service Use Input**

Mothers of the participants will be involved in the development of the study, particularly with the development of the postcard information card and also the design, content and format of the online questionnaire. Research students will interview mothers at the Liverpool Women's Hospital about the aesthetics and format of the questionnaire and postcard. Finalised versions of the questionnaire will be piloted at the Liverpool Women's Hospital. Mothers will be interviewed while completing the online questionnaire. Interview questions will be standardised and prepared prior to seeing the parent. They will be asked to feedback on matters such as appearance and format, ease of completion, and clarity and content of the information and questions.

**Figure 2.6: Gantt Chart Showing Protocol Development and NRES Application Timescale**

This Gantt chart above portrays a more detailed overview of the each process of the protocol development, particularly while developing the protocol, supplementary documents and the NRES application.



## 2.5 Conclusion

The LBCS is a unique birth cohort study that not only maps respiratory symptoms of Liverpool preschool children, but also explores the impact of these symptoms upon the child and their parents. Respiratory disease incurs a significant burden upon the health resources of the UK. Respiratory health in the Liverpool population as a whole is reportedly poor compared to the English population<sup>137</sup>. With persistently high levels of deprivation in the city, figures show that Liverpool remains ranked as the most deprived local authority area in England<sup>148</sup>. Notably, social inequality causes a higher proportion of deaths in respiratory disease than any other disease area<sup>136</sup>. The development of the study protocol required collaboration with experienced paediatricians and a review of previous respiratory and birth cohort studies.



## 3 Application to Ethics

### 3.1 Introduction

#### 3.1.1 Getting Started with IRAS

The Integrated Research Application System (IRAS) is the online system for applying for approval from the National Research Ethics Service (NRES), a requirement for all studies involving NHS Patients. The IRAS E-learning tool was useful as initial guidance. Completion of the IRAS application was a valuable learning process and imperative for the continuation of this study. Collaboration with many departments such as R&D departments, university representatives and Research Ethics Committee (REC) was necessary in order to devise an adequate application for submission to the NRES.

#### 3.1.2 The Importance of Ethical Approval

Every proposal for medical research must be reviewed and approved by an independent ethics committee before it can proceed. Subsequently it was imperative that the LRBCS received ethical approval in order to proceed with the study's development. The World Medical Association (WMA) developed the Declaration of Helsinki, a statement of ethical principles for medical research involving human subjects<sup>176</sup>. These statements must be considered when developing a research protocol. In order to obtain approval, researchers must explain the purpose and methodology of the project; demonstrate how research subjects will be recruited, how their consent will be obtained and how their privacy will be protected. In addition, they must; specify how the project is being funded; and disclose any potential conflicts of interest on the part of the researchers<sup>177</sup>.

Research must also be justifiable on scientific grounds. It is also important that any risks to the research subjects are reasonable and proportionate to the potential benefits of research<sup>176</sup>. Another more controversial factor is the sociological benefit of the study whereby research must provide some benefit to the well being of society as a whole<sup>177</sup>. This however is a subjective matter as not all research benefits the population as a whole but instead only a small minority<sup>177</sup>. However this might be mitigated if the research population, or future populations should benefit from the results of the research<sup>177</sup>. Approval is important, as researchers need to demonstrate to an impartial expert committee that the project is worthwhile, that they are competent to conduct it, and that potential research subjects will be protected against harm to the greatest extent possible<sup>176</sup>.

### 3.2 Factors for consideration

Numerous important ethical issues were considered during the study design.

Among the most important were:-

- Informed Consent
- Data Protection and Storage
- Preventing contact with parents of deceased children

Informed consent is an imperative aspect when partaking in any form of research, but particularly when the research involves children. In this particular case the research involves minimal intervention, particularly with regards to the children involved but consent must be sought from the child's parents or guardians.

Data protection and storage is also an important consideration particularly with regards to confidential details. In the case of this study participant's personal data, in the form of the recruitment postcards will be archived securely at the Institute of Child Health, Alder Hey. The encrypted database will be stored on the University's secure server. No patient/parent identifiable data will be included in publications.

An additional risk identified in previous postal questionnaire studies is the risk of sending questionnaires to parents of deceased children. The Alder Hey Children's Hospital (AH) is notified directly by General Practitioners (GP's), clinical staff from hospices, specialist care teams, and palliative home care teams when a child dies. This allows rapid (near real-time) updating of the AH IT database. Other sources of notification of death comes from regular "batch" searches conducted by Alder Hey IT staff against the NHS Personal Demographics Service. Collaboration between the study team with information analysts at AH enabled the identification of any deceased participants on a weekly basis and will prevent questionnaires being sent to the parents of these children.

The Alder Hey IT department will perform weekly searches using the LRBCS participant data, which returns data regarding deceased children overnight. Searches will be conducted using the local hospital information system, MEDITECH© (Medical Information Technology Inc. Massachusetts USA) to firstly identify the patient's unit number (AH number) using demographic details such as surname, DOB, Postcode. Once matched, the team identify if a date of death has been recorded.

While not foolproof, it was the only practical solution and would enable the research team to update the contact database on a regular basis and avoid contacting parents of deceased children by post or by email. However, it must be considered that there is a delay between AH being notified from the wider community. In addition the 'batch trace' may not pick up all notified deaths particularly as patient details such as name and date of birth need to be matched. Any errors in these details either on the study's database or on AH's database may lead to participants not being recognised. This procedure will help avoid contacting bereaved patients is more robust than the only alternative, which is writing to individual GPs prior to each and every contact. This would make the study virtually impossible to do whilst awaiting replies from GP's. This approach exceeds current best practice in use by routing NHS services.

### **3.3 Study Documentation**

In order to submit an application via IRAS, study documentation must be included. This documentation was prepared in accordance with NRES guidance, with particular attention to aesthetics and is included in the appendix of this thesis.

#### **3.3.1 Participant Information Sheet (PIS)**

This was designed using guidance provided by NRES. This document highlighted the importance of brief, succinct and easily comprehensible phrasing (see appendix 2, figure 8.5). PPI work at the LWH aided with the development of this document, resulting in amendments to the appearance of the document. Amendments included the addition of the images of colourful children as a footer, and prominent sponsor logos as the header.

#### **3.3.2 Participant Recruitment Postcard**

This additional document included important information from the PIS (see appendix 2, figure 8.2). This postcard designed for recruitment, provides a straightforward method to provide patients with information about the study and to collect contact details. The aesthetics and professional appearance of this document were closely scrutinised by the research team and experienced paediatricians, as this is the first document potential participants are exposed to. Feedback gained was used to improve and optimise the design. This document was also subjected to public scrutiny during PPI work by the research team at the LWH. Following this, the design and appearance was edited to include a plain background, larger text, prominent logos and the images of the recognisable children as a footer.

### **3.3.3 Consent Form**

NRES approved mothers check a box then fill in their initials using Adobe Forms Central to indicate their informed consent using the online version of the form. A record of answers received will be saved to a database stored on a secure University server. For those that request paper questionnaires, written consent will be sought using traditional paper consent form designed using guidance provided by NRES (see appendix 2, figure 8.4).

### **3.3.4 Demographic and Exposure Questionnaire**

The decision for which particular demographic and exposure data to use was made using previous studies and followed discussion with senior researchers. Initially a postal questionnaire was drafted and carefully reviewed by senior paediatricians. Questions were drafted following the format of previously validated questionnaires such as the ISAAC Questionnaire, St George's Questionnaire and the Wisconsin Upper Respiratory Symptom Questionnaire<sup>178</sup>. The question regarding ethnicity was formulated using stringent guidance from a number of sources<sup>179-181</sup>. Their recommendations were carefully considered and used to devise an adequate question for collecting data on ethnicity. The final versions of the questions were put together to form a demographic and exposure questionnaire that was then submitted for ethical approval to NRES. During the final design of the questionnaire, after ethical approval, the demographic and exposure questions were combined with the LRSQ questions to form one, relatively brief, questionnaire (see appendix 5, figure 8.7).

### **3.3.5 Power point presentation mock up of proposed online documentation**

This document provided a visual mock up of the proposed online resources (see appendix 2, figure 8.1). It was drafted using Windows Power Point and provided an imitation of the invitation email, demographic questions and the LRSQ in the form of potential slides that the participants might view. Although the online questionnaire had not been developed at this stage, these slides provided the foundations for its development.

### 3.3.6 The LRSQ

Domains of the LRSQ were edited after permission from Professor Shaw. In the second domain “My child has snored” was removed because previous studies showed poor internal validity for this particular question. In addition the question “Has your child ever had wheezing (whistling noise) coming from the chest) at any time in the past?” was removed. This is because the LRBCS is a longitudinal study from birth so would be expected to pick up any symptoms of wheezing from birth making this question unnecessary. The original front page consisted of questions regarding contact and demographic details, these were simply re-ordered following Patient and Public involvement work at the LWH, discussed further in the fifth chapter of this thesis. The final section of the LRSQ is aimed at gathering data concerning treatment and interactions with health care services; the exclusion of this section is highly unlikely to affect the validity of the symptom component of the questionnaire. These questions again were edited during the design of the web-based questionnaire following PPI work at the LWH.

## 3.4 Sponsorship

A sponsor is ‘the organisation responsible for a project’s administration, management and financing (or arranging financing)<sup>182</sup>. NRES states that “all research falling under the remit of the Secretary of State for Health must have a formal sponsor, this includes all research in health and social care that involve NHS patients, their tissue or information’<sup>182</sup>. NRES states that if a co-sponsorship agreement is reached then one body should be nominated as lead sponsor for the purposes of the ethics application and a sponsor letter should be provided describing the responsibilities of each sponsor<sup>182</sup>. In the case of this study, co-sponsorship was secured from the University of Liverpool and the Liverpool Women’s Hospital Foundation Trust. The University of Liverpool agreed to act as this study’s lead sponsor.

### 3.5 Amendments

The study received a favourable opinion in May 2012 following a proportionate review by the West Midlands NRES committee (Reference: 12/EM/0194). Since then, only two applications for minor amendments have been submitted to NRES.

#### 3.5.1 First Minor Amendments

These amendments were initiated during further development of the recruitment strategy and the discovery of additional extras in terms of the software. An optional QR code (two dimensional bar code) that provided a link to an online version of the sign up form using the software Mail Chimp was added to the recruitment postcard. This was proposed as it not only added an additional contemporary method for signing up to the study but also provides an opportunity to assess the viability of this strategy.

To promote the study at the Liverpool Women's Hospital an A3 poster was drafted and designed using information from the postcard. This also includes the sign up QR code. Posters will be displayed on maternity and neonatal wards at the Liverpool Women's Hospital. Prior to NRES application, approval was first sought from Ms Louise Hardman, the Local Research and Development Clinical Trials Coordinator for the LWH, who approved the A3 poster and the use of the QR code.

The information content on the postcard has been approved with only the exception of the QR code, which is also included on the poster (see appendix 2, figure 8.3). This QR is simply a link to an online version of the postcard, which allows patients to sign up to the study electronically. The sign up form includes the same information content as both the postcard and poster.



### 3.5.2 Second Minor Amendments

The following additional amendments were made prior to commencing recruitment (all developed in order to facilitate recruitment). An additional option box has been added to the recruitment postcard for singleton, twins, triplets and other. This change has been added in order to ensure that the research teams identify any babies who have the same mother and date of birth.

The study title has since been revised to include a more comprehensible 'Liverpool Baby Breathing Study' title in addition to the current title 'the Liverpool Respiratory Birth Cohort Study'. This was felt to be a more parent-friendly title. Feedback from parents and midwives concluded that there was some confusion with the current title and that both groups would prefer an additional title that is easier to remember and understand. This will be included on all emails and documents *in addition* to the current title, The Liverpool Respiratory Birth Cohort Study.

A new study website was designed and constructed purely for the benefits of participants and to aid recruitment (<http://pcwww.liv.ac.uk/~lrbc/babystudy.htm>). The content of this website includes details from the patient information documents already submitted to ethics. Patients may sign up via the website to receive regular updates on the study's progress. The website plans to include details on the recruitment process and preliminary study results. In addition, the research team's contact details are available, if participants wish to contact the research team with questions or problems.

### 3.6 Conclusion

Considerable care was taken while preparing the required documentation for ethical submission. Guidance given by NRES and IRAS was reviewed and carefully considered during its development. Ethical approval was given following proportionate review as the LRBCS is considered a 'low risk' as it is an observational study. Co-sponsorship has been secured from the University of Liverpool and the Liverpool Women's Hospital Foundation Trust. Since ethical approval, only two minor amendments have been made.

# 4 Questionnaire Development

## 4.1 Introduction

### 4.1.1 The Truth About Web-Based Questionnaires

In recent years, numerous studies have been conducted in relation to Web based surveys. Since the late 90's, as the popularity, simplicity and potential of the Internet has developed it is easy to see why researchers view the Internet as an invaluable tool for research<sup>183</sup>. Web based questionnaires are a particularly promising method that are less costly, provides more reliable data and has higher response rates<sup>183</sup>. Participant rates in epidemiologic studies have been shown to gradually decrease approximately 1% per year over the last decades, with sharper declines in recent years<sup>183</sup>. Older studies have shown poorer response in web-based questionnaires but since the popularity of the Internet has increased more recent studies have in fact shown higher response rates<sup>184</sup>.

Recent studies have actually shown that the overwhelming majority of respondents preferred the Web-based version to postal questionnaires and telephone interviews<sup>184</sup>. The US Millennium Cohort Study is a successful example of the use of the Internet for epidemiological studies when over 50% of 77,047 participants chose to enrol in the study via the web<sup>185</sup>. This resulted in substantial cost savings to the project<sup>185</sup>. Questionnaire completion rates were, on average 98.3%, for both the web and paper responders<sup>185</sup>. However, web responders provided more complete contact information, including their e-mail addresses<sup>185</sup>. These results demonstrate the value of questionnaire research conducted over the Internet in comparison with traditional postal questionnaire methods<sup>186</sup>.

A search conducted using PubMed, identified 210 articles relating to Internet or online questionnaires and postal questionnaires. This was narrowed down to 48 relevant articles after reviewing titles and abstracts. These articles were subsequently reviewed to identify what current literature has to say about web-based questionnaires versus postal questionnaires and lessons that might be learnt. Literature was further reduced to 33 relevant articles which provide valuable literature regarding web based questionnaire studies and their development, dating between 1998 and 2013 (see appendix 3, table 8.4).

Past studies have noted significantly higher response rates with postal surveys<sup>187</sup>. A 2004 study sending postal surveys to surgeons also demonstrated significantly lower response rate to web based surveys (99/221, 45%) than postal questionnaires (128/221, 58%) (absolute difference 13%, 95% confidence interval (95%CI) 4%-22%,  $p < 0.01$ )<sup>188</sup>. It was noted that researchers should not assume that the widespread availability and potential ease of Internet-based surveys will translate into higher response rates<sup>189</sup>. Fleming et al (2009) found that the web-based survey yields a sample not significantly different than the mail survey in terms of gender, age, income, education and country of residence of respondents, and at a substantially lower cost<sup>190</sup>. Web-based and mail surveys can easily be ignored so getting a reasonable response rate can be challenging<sup>190</sup>. In a German study (2010), the vast majority (328) participants chose to use Web-based questionnaires rather than the traditional postal survey (139)<sup>191</sup>. In a 2010 survey of smokers 438 (63%) chose to receive a mailed paper survey and 259 (37%) chose an Internet survey, although return rates were the same for both modes (92% versus 92%,  $p = 0.82$ )<sup>192</sup>.

In comparison, a more recent study by Atherton et al (2010), where participants were contacted by email after 12 months and given a web link to an online questionnaire or sent a postal questionnaire response rates were 51% and 29% 4 weeks after (Relative Risk (RR) 1.78 (95%CI 1.47 to 2.14)) and 72% and 59% after three months<sup>189</sup>. In this young student population, an online questionnaire was quicker, cheaper and more efficient than a postal questionnaire but some college students did not have an email address<sup>193</sup>.

In the contrasting elderly population, web-based response rates are substantially reduced<sup>194</sup>. In a hip replacement study (2011), response rates differed significantly ( $p < 0.001$ ) between both groups, with a 92% response in the pen-and-paper group and a 49% response in the web-based group<sup>194</sup>. A 2010 study showed that web response was greatest at younger ages, with 20.9% of those aged <30 years responding<sup>195</sup>. This declined with age as 3.6% of women aged 60 years or more responded<sup>195</sup>. Web questionnaires were filled out more completely than paper questionnaires, regardless of the sensitivity of a question<sup>195</sup>.

In a 2006 study investigating testicular cancer, participant nonresponse was significantly higher among participants who chose the postal questionnaire<sup>196</sup>. The proportion of questionnaires with missing items and the mean number of missing items did not differ significantly by mode<sup>196</sup>. Compared with postal questionnaires, online questionnaires were returned significantly more quickly and required significantly fewer reminders<sup>196</sup>. Online questionnaire completion can be offered in a cancer sample without compromising data quality<sup>196</sup>.

Web-based questionnaires offer potentially substantial cost savings but past studies show that this needs further evaluation<sup>184</sup>. These savings are because the costs for printing questionnaires, postage, and data entry are avoided<sup>184</sup>. A study by Russell et al showed that the cost of developing and processing a returned paper questionnaire was four times that of a returned Web questionnaire, primarily because of return postage costs and greater processing time for paper questionnaires<sup>197</sup>. However the set-up costs, including Web site and survey design, may be substantial, particularly for very large studies, so this must be evaluated<sup>184</sup>. Those that invited participants through e-mail reported cost benefits associated with using Web-based questionnaires<sup>184</sup>. The relatively low cost of web-based questionnaires advantageous as it enables large sample sizes, thus providing an increased potential for sub-group analysis and decreased sampling variance<sup>198</sup>.

The speed and accuracy of web-based data collection is superior to postal questionnaires<sup>199</sup>. Not only is data collected using web-based questionnaires better quality but it is also much more complete<sup>199</sup>. Validation checks can be incorporated with prompts that alert respondents when they enter implausible or incomplete answers<sup>184</sup>. Web questionnaires are also more rapidly returned, even at least twice as quickly as postal questionnaires<sup>196</sup>. Email systems are superior to the postal in terms of speed of data collection<sup>187</sup>.

Some studies suggest that fewer reminders are needed for online questionnaire return because the majority of online questionnaires were returned before the first reminder<sup>193, 196</sup>. Ritter et al also found that Internet questionnaires required fewer follow-ups to achieve a slightly (non-significant) higher completion rate compared to mailed questionnaires<sup>200</sup>. However other studies showed that more frequent reminders were essential in obtaining a good response rate<sup>187</sup>. Telephone prompts and postal questionnaires were also useful for higher response rates<sup>197</sup>. Regardless of the type of questionnaire reminders are effective and have been shown to increased recruitment by around 4% for each reminder sent for both invitation methods<sup>197</sup>. Email invitations were shown to be simpler and cheaper to use, despite not affecting response rates<sup>197</sup>.

One of the main issues with web-based questionnaires that researchers should be aware of is the potential sampling bias created by more highly educated participants and managers/professionals choosing to complete online questionnaires<sup>196</sup>. However, this is unlikely to cause problems if both postal and online questionnaires are offered and can be adjusted for by weighting in some circumstances<sup>196</sup>. Researchers must recognise that younger patients are more likely to use online sources of information and return web-based questionnaires<sup>201</sup>. In a study by Lusk et al (2007), web-based respondents were younger, and worked fewer years in healthcare, and were more likely to be male and to work in a hospital<sup>202</sup>. Mayr et al (2012) also concluded that participants using the Internet were younger, better educated, and more often male compared with participants preferring the paper version<sup>191</sup>. Despite this, after adjusting for these differences, investigators found no additional direct effect of web-based data collection on any of the outcome variables<sup>191</sup>. A more recent study by Danon et al (2013) noted a clear difference between the age of participants who completed the web survey in comparison to those who completed the postal one, the average age being 37 and 56 respectively<sup>203</sup>. These factors will certainly be considered during the development of the LRBCS.

Mixed-mode surveys have also been conducted, that involve the application of a mixture between postal and web based questionnaires<sup>204</sup>. They are viewed as an alternative method to postal surveys that produce comparable response rates at lower costs<sup>205</sup>. Combining a web-based questionnaire with a traditional postal follow-up questionnaire (mixed-mode survey) could possibly compensate for the previously noted weaknesses of completely web based surveys and provide an alternative to a postal survey<sup>204</sup>. A study by Beebe demonstrated that an initial mailing of a self-administered form followed by a web survey to non-respondents provided a non-significantly higher response rates and a more representative sample than one that started with a web-based form and ended with a mailed survey (71% vs. 62%,  $p=0.07$ )<sup>206</sup>.

A web-based system is not without its flaws. Electronically distributed questionnaires require correct email addresses as well as access to computers and the Internet for successful deployment<sup>187</sup>. Mailed and electronically distributed questionnaires do, however, give participants time to think about their responses to questions, but may require telephone or helpline assistance to be available for participants<sup>187</sup>. In a study by Braithwaite et al on general practitioners 26% of the email invitations sent were rejected by the server due to incorrect or invalid e-mail addresses<sup>197</sup>. A summary of the pros and cons of have been summarised below (table 4.1).

**Table 4.1: Summary of pros and cons of web-based questionnaires**

<i>Pros</i>	<i>Cons</i>
Higher response rates	Concerns regarding response rates
Less costly as costs for printing questionnaires, postage, and data entry are avoided	Set up costs may be required for web site and survey design, which can be substantial
Better quality data that is more accurate e.g. less missing data	Concerns regarding the reliability and validity of the data obtained
Accessibility is increasing as popularity of the internet ha increased and technology such as smart phones allow access.	Limited accessibility for a subset of the population without access to the internet or emails
Emails systems allow quick delivery of questionnaires and are cheaper and quicker to use	Correct email addresses needed
Some respondents prefer these form of questionnaires particularly the younger population	Some respondents prefer postal questionnaires, particularly the older population
Online survey software enables fast data collection in real time	Safety and confidentiality issues and participants perception of these
Easier to monitor response and problems with delivery	Respondents may not check their emails as frequently as their post
Fewer reminders, and if needed these are easier to carry out	Some studies report that more frequent reminders needed
Any sampling bias can be weighted	Sampling bias due to respondents being more highly educated and from a younger population.



Nonmonetary incentives, such as lottery participation and survey results may significantly improve response rates<sup>184</sup>. In a study by Wilson et al, knowledge of a financial incentive did not significantly increase the response rate to an online questionnaire<sup>207</sup>. It was concluded that future studies should consider including a randomized element to further test the utility of offering incentives of other types and amounts to participate in online questionnaires<sup>207</sup>.

Additional factors that improve response rates have been summarised in table 4.2 below.

**Table 4.2: Factors that improve response rates in web surveys**

<b>Factor</b>	<b>Example/ description</b>
<b>Nonmonetary incentives</b>	These include Lottery participation and survey results <sup>184</sup> . Lottery participation seems to be the most effective for short questionnaires <sup>208</sup> .
<b>Monetary incentives</b>	A money based reward such as gift vouchers e.g. Amazon seem the most effective for long questionnaires <sup>208</sup> .
<b>PDF version</b>	Providing an additional pdf option to give patients a choice <sup>184</sup>
<b>Careful use of design elements</b>	Text, format of questions, images, colour, graphics <sup>184</sup>
<b>Style of questions, number of pages</b>	Minimal pages and readable format of questions. Prompts to certain questions to improve understanding <sup>198</sup>
<b>Alternative postal option</b>	Minimise sample bias and offer participants an choice <sup>209</sup>
<b>Email invitation</b>	Emailed invitations to join a study or emails including URL links to a questionnaire improve response rates as opposed to mailed invitations or online recruitment <sup>210</sup>
<b>Reminders</b>	Frequent reminders improve response rates <sup>187</sup>

The main advantages of using electronic surveys are their relative ease of implementation, and the potential to conduct large-scale surveys whilst eliminating the costs of stationery, postage and administration<sup>197</sup>. Simple questionnaires do not require extensive programming skills or time particularly with the help of modern survey software<sup>197</sup>. Responses from online questionnaires can be automatically and easily inserted into spreadsheets, databases or statistical packages<sup>197</sup>. Not only does this save time and money, but also reduces missing data during completion and human error in data entry and coding<sup>197</sup>.

Data can also be collected continuously, in the participants' own time, regardless of time of day and day of week, and without geographical limitation<sup>198</sup>. Prompts to certain questions can alert respondents if they don't understand, skip or incorrectly answer questions<sup>198</sup>. Drop-down boxes provide participants with a range of possible answers, questions can be ordered randomly, conditional questions can be included, skip patterns may be built for ease of navigation, even multilingual formats are possible<sup>198</sup>. As one study pointed out, the growth in e-mail, online banking and bills being paid on the Internet suggest that, at least for some people, the Internet is a more convenient medium than traditional means of communication<sup>198</sup>.

Interactivity in the web questionnaire increased compliance in completion of the second section of the questionnaire<sup>211</sup>. The order in which respondents see specific questions can be controlled, preventing respondents from returning to change their answers<sup>197</sup>. Although automated systems of electronic entry of data into a database exist for paper-based surveys, these are relatively expensive<sup>197</sup>. However, web-based questionnaires allow simple automatic transfer of data into a database, thus eliminating the need for manual inputting and avoiding potential errors of data entry<sup>197</sup>.

Although scarcely used in epidemiological research, the advantages and disadvantages of web-based questionnaires, particularly in comparison to the more traditional postal questionnaire method have more recently been widely documented<sup>184</sup>. Currently developments in web-based questionnaires are very promising but considerable care must be implicated when designing studies around this method<sup>184</sup>. Internet research offers many advantages but as numerous studies highlight, further research is required into methods to improve the external validity of web-based questionnaires<sup>184</sup>. This includes approaches to increase the representativeness of study samples and limit response bias<sup>202</sup>.

Past studies have noted that the general population has yet to become more familiar with the Internet before an online survey can be the first choice of researchers<sup>133</sup>. However the web-based method is worthwhile considering within selected populations as it saves resources and provides more complete answers<sup>212</sup>. The Internet is an ever-developing field and as online banking, payments, booking and searching becomes increasingly popular and it is likely web-based questionnaires will follow the trend<sup>209</sup>. Assuming the interface is well designed and user-friendly, many patients were happy to use the Internet to answer questionnaires<sup>209</sup>. As current literature shows, it is not yet time to completely abandon paper<sup>209</sup>. But alongside a traditional paper questionnaire to minimize sample bias, a web-based questionnaire is certainly a very promising option<sup>197</sup>.

#### 4.1.2 Web-based Questionnaires and the LRBCS

The creation of an online equivalent of the LRSQ was essential in order to facilitate emailing versions to participants. A portable document format (pdf) version was not considered due to the major limitations of this method in terms of design, usability, response rates and ease of return. Instead the research team opted for a questionnaire that may be completed online, rather than one that needed to be returned by email. There are many advantages to this method that include rapid data collection, faster return, cost savings, less missing data/ more complete data and relative ease of implementation. However online surveys are not without their limitations such as sampling bias, required email addresses and computer literacy, which may lead to poorer response rates.

In order to produce an online version of the questionnaire, survey or form filling software is needed. Survey software needs to be acceptable in terms of freedom to design and usability for researchers to ensure the success of the LRBCS. In addition, the survey software needs to be practical and usable for all participants. Software that has the scope to edit all elements of design and appearance is essential. To ensure that the most appropriate, cost effective and adaptable software is used, several different software options were identified. These were explored and trialled by the research team to evaluate their potential for use in this study.

## 4.2 Justification of Software

### 4.2.1 Survey Software Options

Numerous survey building software options were identified and have been summarised (table 4.3). Both form and survey building software provided a potential platform for developing an online questionnaire. All software options were evaluated in terms of usability, freedom of design, deployment method, cost and online security. Many of these were excluded on the basis of price, usability, security and post-purchase support (table 4.3)

**Table 4.3: Survey Building Software Trailed**

<i><b>Survey Software</b></i>	<i><b>Form Software:</b></i>
KwikSurvey, Qualtrics (and Surveyz), SurveyBuilder, Survey Expressions, Survey Gizmo, Smart-Survey, SelectSurvey.NET, Survey Methods, Survey Monkey.	Adobe FormsCentral, EmailMeForm, FormBuilder, Formsite, Google Docs, WordPress, Wufoo.

Of the software summarised (table 4.3), four software options demonstrated potential for use in this study and were explored further. A comparison of these options has been summarised below (table 4.4). Among these are SelectSurvey.Net (SS), SurveyMonkey®, Google Docs and Adobe® Forms Central (AFC). The table clearly displays that SS and AFC are the superior options and the most desirable for use in the LRBCS.

**Table 4.4: Comparison of Survey Software (courtesy of B. Griffith)**

<b>Annual Cost</b>	<b>Survey Monkey</b>	<b>Google Docs</b>	<b>Adobe Forms</b>	<b>Select Survey</b>
	£299	Free	£105.39	University
<b>Design Usability</b>	Good	Good	Excellent	Fair
<b>Formatting Appearance</b>	Templates	Templates	Unlimited	Templates
<b>Skip Logic Question</b>	Yes	No	Yes	No
<b>Answer Piping</b>	Yes	No	No	Yes
<b>Answer Pre-Population</b>	Some	No	No	No
<b>Help text</b>	No	Limited	Yes	No
<b>Logos and / images</b>	1	No	Unlimited	1
<b>Field Validation</b>	Yes	No	Yes	Yes
<b>Integrated email</b>	Limited	No	No	Limited
<b>Security System</b>	SSL Encryption	Data cloud	SSL encryption	Encrypted
<b>Data Export</b>	Yes	Yes	Yes	Yes
<b>Statistical analysis</b>	SPSS export	Excel export	SPSS export	SPSS export
<b>Data Summary</b>	Yes	Yes	Yes	Yes
<b>Progress Bar</b>	Yes	No	Yes	Yes
<b>Support Available</b>	Email	No	Both	Via UoL

#### 4.2.2 SelectSurvey.Net vs Adobe Forms Central

Following software comparisons, the research team concluded that the best options would be either SelectSurvey.NET (SS) or Adobe® FormsCentral (AFC). The former is secure and available free through the University of Liverpool, but has limitations in terms of formatting<sup>213</sup>. The latter is very easy to use with freedom of design, but has moderate cost implications<sup>214</sup>. Both software options have their benefits and limitations, which are discussed later in this chapter.

It was particularly important to ascertain the security of both survey software before either were considered for use in the LRBCS. Both software options offer layered security services. AFC is Secure Sockets Layer (SSL) encrypted and is hosted on a hypertext transfer protocol secure (https) server<sup>214</sup>. HTTPS is a protocol for secure communication over a computer network with particularly wide deployment on the Internet, while SSL provides additional data security layered under https<sup>215</sup>. SSL is a encryption technology that encodes information from the client machine to make it meaningless if it is intercepted in transit and is designed to enable web-sites to pass sensitive information securely<sup>216, 217</sup>.

SS claims to have seven security levels, which include, SQL injection protection. SQL injection is a technique often used to attack data driven applications and exploits a security vulnerability in an application's software<sup>218</sup>. SS is also hosted on a https server provided by the University of Liverpool<sup>213</sup>. Both survey software offer adequate security levels for this study's requirement. Feasibility testing conducted at the LWH was deemed the most appropriate method to determine which survey software should be used for the study. Mothers were asked to complete both versions of the initial questionnaire designed using both forms of software and comment on appearance, usability, format and readability, before indicating their overall preference. The process and results of the feasibility testing are discussed in chapter five of this thesis.

### 4.3 Mailing software

An imperative part of this study's methodology is the deployment of questionnaires. In order for this to be feasible and practical, an automated scheduling emailing system was needed. Emailing a link to participants is reportedly the best method to deploy online questionnaires<sup>219</sup>. None of the survey software options that the research team explored had an integrated and automated emailing system that would be suitable for the LRBCS. Some of the mailing requirements of the study could be met with a simple email merge but this would require date calculations to be entered for each participant. This is time consuming, impractical, and could result in human error leading to surveys being sent at incorrect dates, particularly as potentially 8,500 participants may be recruited each year as part of the maximum recruitment strategy. Mailing using email merge would also rely upon an individual's personal computer being switched on at the specified date and time to allow emails to send, which is also highly impractical.

Many email scheduling software options identified would significantly burden the study financially, with prices ranging from \$75 - \$500 month. Email scheduling software includes Constant Contact®, Pinpoite, Inc, iContact LLC, Benchmark Email (Benchmark Internet Group), MailChimp®, GetResponse®, Mailigen®, Vertical Response Inc, Mad Mimi LLC, GraphicMail Ltd, Campaigner® and Chaos Intellect, Inc. Options that were not web based and required downloading a software package would not be practical with large and changing research team. In addition, these programmes require a computer to remain switched on in order to process emails. This is both costly and impractical, especially when web-hosted options offer a convenient and accessible alternative. After researching numerous email management services, it was decided that MailChimp® offers the most efficient system to meet the needs of this particular study.



### 4.3.1 MailChimp®

This email management system host's email lists on a secure online server and allows automated emails to be sent regardless of whether the researchers computers are on. This fully automated service schedules emails at specific intervals from the information held in its database such as child's date of birth, without the need to calculate dates. A member of the research team may set up all future emails as soon as participants have consented to be contacted by the study team. Potential participants may provide consent to be contacted either by completing their details on the recruitment postcard. Emails may be scheduled to send at specific intervals, thus ensuring invitations for survey completion are deployed at precisely the correct time point to the participants.

An additional feature, particularly useful for the LRBCS, is the option to create a sign-up Quick Response (QR) Code<sup>220</sup>. This two-dimensional bar code stores a Uniform Resource Locator (URL) that can be read using a Smartphone application. Once scanned, the code links to an online sign up form to the LRBCS. Once completed, the research team are notified, and participants are automatically subscribed to the study list and are subsequently sent the questionnaire at the relevant time.

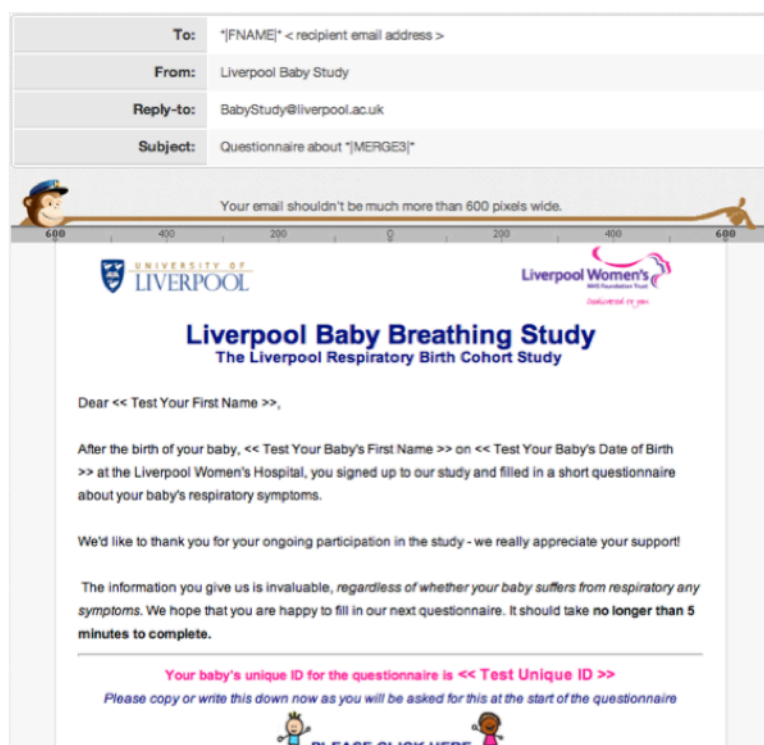
The research team are also able to track individual participants actions with regards to opening emails, number of times emails are opened and if the URL link to the survey had been clicked<sup>221</sup>. This intelligent software displays the time and date participants open emails<sup>221</sup>. The overall "open-rate" is calculated as a percentage in addition to the percentage of participants who have clicked on the link<sup>221</sup>. These features allow the team to recognise poor response rates or any increases in dropout, and will therefore allow them to address the root of these issues promptly<sup>221</sup>.

Recipients may employ autonomy by 'unsubscribe' themselves from the mailing list<sup>221</sup>. This addresses the right of participants to withdraw from the study at any time, consistent with ethical approval. In addition the technology allows the research team to ask participants to specify their reason for

leaving the study. Reports are emailed in real time to the research team detailing which participants have removed themselves from the study and why they have

chosen to do so, again identifying the research team to identify problems promptly<sup>221</sup>. An additional valuable feature is the option to pipe participant's details not into the email contents but also into the email subject box. This

**Figure 4.1: Preview of an Email Drafted by MailChimp®**



enables the research team to send personalised emails that the respondents see as soon as they appear in their inbox, instead of only while reading the email.

With regards to security, MailChimp® is hosted on an HTTPS secure server and is SSL encrypted<sup>222</sup>. Passwords are encrypted and distributed denial of service (DDOS) mitigation is in place at all data centers<sup>222</sup>. DDOS are attempts to make a machine or network resource unavailable to its intended users, such as efforts to temporarily or indefinitely interrupt or suspend services of a host connected to the Internet. All these measures ensure participants' details are safe and secure.

The format and design of the emails themselves are also easily modifiable<sup>221</sup>. The study sponsors' logos (LWH and UoL) may be applied in addition to the colourful children footer, consistent with the questionnaire design (see figure 4.1). This maintains a professional appearance that may be easily recognised by participants. With unlimited merge fields, the research team

can personally address emails to parents, using their child's name and the unique identification number<sup>221</sup>. Replies to these automated emails can be forwarded directly to the research teams' email address allowing the research team to address any questions, feedback or issues the participants may have<sup>221</sup>.

MailChimp® abides by the United States, CAN-SPAM Act (2003) and requires its costumers to do the same<sup>223</sup>. As a result emails sent by this intelligent software will not appear in the recipients junk folder. MailChimp® also provides guidance for avoiding spam filters and reduces points appointed as part of spam filters criteria<sup>224</sup>. In addition MailChimp® offers an Inbox inspector that enables clients to test email 'campaigns' and thus reducing the chances that emails are sent directly to recipients junk/trash folder, resulting in a lower open rate and subsequently fewer responses<sup>225</sup>. MailChimp® regulations also reflect those of UK spam laws for Electronic Communications, the Privacy and Electronic Communications (EC Directive) Regulations 2003<sup>226</sup>.

Overall, MailChimp® is an essential component for the deployment of the online LRSQ. Not only does the mail-scheduling feature reduce administrative error with regards to deployment of the questionnaire, but also features such as reducing spam score are imperative to the success of the online side of the LRBCS.

## 4.4 Developing the Online Questionnaire

Prior to feasibility testing, two separate questionnaires were developed using both SelectSurvey.Net and Adobe® Forms central. This allowed the usability, design options and any limitations of the software to be thoroughly investigated.

### 4.4.1 Design Considerations

Optimal design of web surveys is essential in order to maximise the benefits of such a rich audiovisual and interactive self-administered medium<sup>227</sup>. However this must be done in a responsible and informed manner<sup>227</sup>. Since the ever-developing worldwide-web evolves at a fast pace, literature surrounding the Internet becomes dated very quickly. The Internet offers new possibilities for the implementation of questionnaires. However this also comes with a numbers of issues that included the complexity of survey software, respondents' computer experience, browsers, speed of access, possibly security issues and complexities with operating systems configurations<sup>228</sup>. A review of current literature on developing and designing questionnaires, particularly those that are web based, found that a number of factors regarding questionnaire design influence participant responses<sup>229</sup>. Factors include, the topic of the survey or study, advanced graphics, instructions for completion and layout<sup>229</sup>.

Respondents may not actually view the questionnaire as was intended by the designer due to differences between web browsers, operating systems, screen configurations<sup>230</sup>. This can compromise the aesthetics, particularly images and colours of the questionnaire. A progress indicator is an additional function suggested from user comments in one survey<sup>229</sup>. Software can place constraints upon the layout and possibly the content of online surveys and they take longer to design than postal surveys, highlighting the importance of correct software selection. HTML surveys enhance response rates because of improved aesthetics with colour usage; screen design and question formatting such as skip logic and conditional questions<sup>231</sup>.

Concerns have been raised over Matrix style questions as response bias has been reported<sup>232</sup>.

Matrix style questions are two-dimensional version of a multiple choice question type with selection boxes or circles. They are arranged in a table-like format with the

**Figure 4.2. Example of Matrix Style Question**

1. When my child has had a COLD in the last three months:

A rattly chest is a noise that you can hear and feel as a vibration, when placing your hands over your child's chest.  
A wheeze is a whistling noise coming from the chest.\*

	Not at all	A few days	Some days	Most days	Every day
My child has had wheezing (whistling noise coming from the chest):	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
My child has coughed:	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
My child has had a rattly chest:	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
My child has been short of breath:	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

questions listed to the left and the answer choices across the top (see figure 4.2). Survey software advise minimal use of matrix questions as they increase survey complexity with regards to appearance and completion<sup>233</sup>.

In comparison, drop-down style questions are less complex and are useful when many choices are provided. This question type offers respondents multiple choices in a dropdown list format and requires the selection one response (see figure 4.3).

**Figure 4.3. Example of Dropdown Style Questions**

**During the NIGHT (when asleep):**

My baby has been wheezing:\*

☒ Not at all
 ☐ A few nights
 ☐ Some nights
 ☐ Most nights
 ☐ Every night

My baby has been short of breath:\*

Literature suggests that it is important to consider technical requirements such as browser requirements, technology used as mode of access<sup>232</sup>. In addition, questionnaires must be trailed thoroughly before they are made available to participants<sup>232</sup>. Recommendations have been made to employ filter questions to prevent participants from having to complete unnecessary questions<sup>232</sup>. It is important to ensure respondents reply only once<sup>234</sup>. A unique identifier is reportedly the most effect method for preventing or identifying multiple responses<sup>235</sup>. Alternative methods would be to compare host names or Internet protocol (IP) addresses of submissions<sup>236</sup>. However

this requires knowledge of how these addresses are assigned on each network to make effective use of this technique<sup>236</sup>.

Clear understanding of the target audience is important to design an appropriate questionnaire<sup>237</sup>. Limited use of images, charts and graphs reduce the questionnaire download time<sup>237</sup>. However careful use of images can provide a context for questionnaire without having to read extra text<sup>237</sup>. Advanced graphics may improve respondents' motivation and satisfaction<sup>237</sup>. Carefully selection of font and consideration of font size ensures readability<sup>237</sup>. Navigation guides such as progress bars are useful tool to help participants complete the survey without getting discouraged or lost<sup>237</sup>.

#### **4.4.2 Software advantages and limitations**

Designing questionnaires using both SS and AFC provided an opportunity to clearly assess advantages and limitations of both survey software. The usability of SS was significantly poorer than AFC. Designers had to edit colour, images, font etc on a separate screen without being able to view immediate results. In addition, only one image may be added, including logos (see figure 4.4). AFC in comparison, enabled users to easily design questionnaires using a drag and drop editor. In addition questions may be copied and pasted and therefore easily duplicated<sup>214</sup>. In addition AFC allows a test drive function, which ensures that the questionnaire may be completed smoothly, and data collections function efficiently<sup>214</sup>. Forms are easy to personalise with any number of logos or pictures<sup>214</sup>. A useful function is the ease to create a PDF version, create conditional questions and 24-hour easily accessible support. A PDF version is a particularly valuable asset as this can then be printed and sent as a paper copy identical to the online version of the questionnaire. In addition it is possible to collaborate with other users to create forms<sup>214</sup>. AFC is very customisable, as far as changing backgrounds, colours, fonts, and adding images are concerned<sup>214</sup>. The software also enables users to create multiple types of questions and copy and paste multiple form elements<sup>214</sup>.

Figure 4.4: Example of the Finalised, SelectSurvey.NET-Version




## The Liverpool Respiratory Birth Cohort Study

[Page 1](#) [Page 2](#) [Page 3](#) [Page 4](#) [Page 5](#) [Page 6](#) [Page 7](#) [Page 8](#) [Page 9](#) [Page 10](#)

Page 5 of 10

### A Few Questions About You and Your Household

- Do you, your partner or your other children (excluding the child this questionnaire is about) have any medical history of hay fever, asthma or eczema diagnosed by a doctor?\*

☐ Yes  
☐ No

- If you answered yes to the previous question. Please tell us which members of your family have these conditions (excluding the child this questionnaire is about).

	Yourself (mother)	Your Child's Father	Your Eldest Child	Your 2nd Eldest Child	Your 3rd Eldest Child	Your 4th Eldest Child	Your 5th Eldest Child
Asthma	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Eczema	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hayfever	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

- Does anybody in your household smoke at all, anywhere?  
(A household member is anybody who sleeps in your house or takes regular meals at your house) \*

Nevertheless, SS software does include basic emailing software, this allows users to control mailing lists but does not include any form of automated email scheduling<sup>213</sup>. Although answer piping is a feature offered, text must already be included at the start of the survey and this is difficult to set up<sup>213</sup>. Piping is a technique that involves automatically including a previous answer in the questionnaire as part of a subsequent question. For example if the participant entered their name as 'Mrs X', subsequent questions would automatically include the participants name 'Mrs X', making the questionnaire more personal. In addition, a previously selected answer may be 'piped' as new answer choice in a follow-up or future question. A benefit of this type of survey is that it offers unlimited responses per survey<sup>213</sup>. Skip logic is available but only using pages, not individual questions. In addition piping is possible from previous answers but this is complicated to put into practice<sup>213</sup>.

A limitation of AFC is that there are a restricted number of responses perform. Creating multiple forms can rectify this and all responses can be imported on a single datasheet. In order to link all data for longitudinal analysis a unique ID will be given to each participant to minimise errors that might occur with multiple forms. Although SS allows page condition logic, individual conditional questions are complex to construct and very basic. Question libraries appear to be a useful function but in reality questions need to be designed in the library. AFC allows simply copying and pasting questions even between different forms. Support for SS is not as useful or available as their website claims but computing staff at the UoL were able to assist with any issues or problems<sup>213</sup>.

Once the questionnaires had been designed, both survey options were trialled using different browsers such as Internet Explorer, Safari, Firefox and Google Chrome. The appearance of both questionnaires did not differ. Literature also highlighted the importance of considering participants mode of access such as using a laptop, mobile, tablet or a personal/desktop computer (PC). Many participants may have limited technology to access the Internet so it is important that questionnaires may be completed using as many modes of access as possible.

Time stamps collected by AFC allowed establishment of the exact dates and times at which participants completed their surveys. In combination with MailChimp® , which records times participants open the questionnaire, this data allows the average time to complete of the questionnaire to be calculated. SS records date of response but not the time completed<sup>213</sup>.

Clearly both the survey software options identified have advantages, and limitations. It was decided that the most efficient and diplomatic way to evaluate the optimal software would be to use potential participants of the study, the mothers at the Liverpool Women's Hospital. This would be conducted in the form of feasibility testing.



## 4.5 Conclusion

Online survey software and email scheduling software are imperative for development, deployment and success of the online LRSQ. MailChimp® has proved to be the most efficient method for emailing participants, particularly with it's automated scheduling options. SS and AFC were concluded to be the most practical measures to design and carry out the questionnaire survey. Feasibility testing at the LWH will ascertain the most effective survey software for the LRBCS.

# 5 Feasibility Testing

## 5.1 Introduction

### 5.1.1 What are Feasibility Studies?

A feasibility study may be defined as a preliminary study to determine a project's viability<sup>1</sup>. They are used to estimate important parameters needed to design the main study<sup>1</sup>. Another definition for feasibility studies is the “analysis and evaluation of a proposed project to determine if it is technically feasible in addition to being possible to conduct within the constraints of the proposed cost”<sup>238</sup>. These studies may be used to evaluate potential recruitment and follow-up strategies in order to maximise response rates<sup>191</sup>. In addition to aiding the design of a suitable outcome measure such as standardised questionnaires<sup>239</sup>. Crucially, feasibility studies do not evaluate the outcome of interest as this is left to the main study<sup>239</sup>. Important parameters they may be determined by these studies are outlined in figure 5.1.

**Figure 5.1: NETSCC Summary of Important Parameters that May be Established by Feasibility Studies<sup>1</sup>**

- Standard deviation of the outcome measure, which is needed in some cases to estimate sample size
- Willingness of participants to be randomized
- Willingness of clinicians to recruit participants
- Number of eligible patients
- Characteristics of the proposed outcome measure or designing a suitable outcome measure
- Follow-up rates, response rates to questionnaires, adherence/compliance rates, etc.

It is important to distinguish between feasibility studies and pilot studies, particularly as studies labelled feasibility studies are reportedly conducted with more flexible methodology compared to those labelled 'pilot'<sup>1</sup>. Feasibility studies are allegedly conducted with a more flexible method strategy and are used to determine the initial viability of a study method<sup>239</sup>. In comparison, pilot studies are smaller versions of the main study that test if the components of the main study are viable<sup>239</sup>. They also provide an opportunity to estimate the study's sample size<sup>240</sup>. In the case whereby the pilot is the first phase of the study and data contributed to the final analysis, this constitutes an internal pilot<sup>240</sup>. Alternatively at the end of the pilot study the data may be analysed and set aside, this is labelled an external pilot<sup>240</sup>. A pilot study and pilot work may also be differentiated<sup>240</sup>. Pilot work may be described as any background research to inform a future study, while a pilot study has specific hypotheses, objectives and methodology<sup>240</sup>. A pilot trial is a stand-alone pilot study and includes a randomization procedure<sup>241</sup>.

Pilot studies are reportedly conducted with more rigorous components such as sample size estimation, randomization and control group selection compared with studies labelled 'feasibility'<sup>239</sup>. This is reflected in current literature, which showed that the majority of pilot studies were full studies run with smaller sample sizes to test out a number of methodological components and clinical outcomes simultaneously<sup>239</sup>. In comparison, feasibility studies tended to focus on fewer methodological components within individual studies<sup>239</sup>. It must also be noted that the MRC guidelines explicitly suggest that preliminary studies, be used preceding major trial which seeks to evaluate a package of interventions, rather than a single intervention<sup>242</sup>.

### 5.1.2 What is the Importance of Feasibility testing?

Feasibility testing provides a secure basis for developing and designing clinical studies. This is particularly important in an era when public health is moving towards evidence-based interventions. In order to accomplish and facilitate this, the need to select, adapt and evaluate such interventions is important. Feasibility studies are able to produce a set of findings that help determine whether an intervention has reasonable efficacy for use in a chosen study. Particularly with regards to outcome measures such as questionnaires, feasibility tests are a valuable method of evaluating the use of such measures and their suitability for the study and its population of interest.

### 5.1.3 How does this link in with the LRBCS?

In order to maximise the success and impact of the LRBCS, the research strategy must be of sound methodology. Both patient and public involvement (PPI) and feasibility studies have been identified as a constructive means to improve recruitment, response rates, attrition and overall reaction to the study<sup>243-245</sup>. As the usability of the questionnaire is imperative to the success of this study, therefore the evaluation of this outcome measure within the population of interest is advisable. Feasibility testing may be conducted before a pilot study or the study itself may begin. The benefits of involving of the patients and public have proven valuable and may be conducted by feasibility testing<sup>244, 246</sup>. It will enable the study team to identify prospective barriers for the study. This is particularly important, as the study will be primarily conducted online, so the accessibility and acceptability of the online questionnaire is important to ascertain.

## 5.2 LRBCS: Patient and Public Involvement

### 5.2.1 Aim

To assess the accessibility and acceptability of the online Liverpool Respiratory Birth Cohort Study in terms of presentation, format and appearance by means of Patient and Public Involvement.

### 5.2.2 Introduction

The design, appearance and format of a questionnaire influences both participation and response rates<sup>229, 247-249</sup>. Literature identified important layout and content factors to consider. The questionnaire introduction must outline the purpose of the study clearly; include details on use of the information<sup>247</sup>. Questions must be clear, simple and as short as possible, with demographic questions placed at the end of questionnaires<sup>250-253</sup>. Similar questions should be grouped together and general questions should precede specific questions to minimise conditioning<sup>249, 254</sup>. Relevant graphics and logos are useful as they remind participants about the purpose of the research<sup>247</sup>. Page density and readability are additional important factors, as too much information per page may confuse respondents, as might poor quality language<sup>247, 248</sup>.

Key factors affecting participants' perception towards a questionnaire are, the layout, order and density of the questions and information given, colour usage, backgrounds, images, logos, and variation in font<sup>248, 249, 254, 255</sup>. One method of identifying important design and appearance elements for questionnaires used in a particular cohort is by patient and public involvement (PPI). PPI is a practical method that involves patients and potential participants during the development of research and its use is increasing particularly in the UK<sup>256</sup>. PPI has evolved significantly as patients and the public have taken an increasingly more active role in the development of clinical research<sup>256</sup>.

PPI has become a key process in strengthening support for clinical research and improving delivery, particularly within the UK<sup>256</sup>. Regulatory bodies such as the Department of Health<sup>257</sup> and the National Institute of Health Research<sup>258</sup> recommend PPI. The development of PPI within Clinical Research Networks is an example of its integration into major research initiatives<sup>256</sup>. Furthermore, the National Institute of Clinical Excellence (NICE) implemented PPI in research and development<sup>259</sup>.

Public involvement reportedly improves recruitment as community members know how best to motivate and encourage their peers and is considered particularly valuable in qualitative research<sup>244</sup>. Involving the public when deciding how to collect information in studies improves response rates, in addition to making research more accessible to potential participants<sup>244, 260</sup>. Feedback from participants can address potentially significant flaws in the study method. As Henley et al described, “‘Patients played a pivotal role in providing ‘front line’ intelligence on how the trial was being received during its development and execution”<sup>243, 244</sup>. Literature has shown that PPI has led to improvements in the design of research tools such as questionnaires and interview schedules<sup>244</sup>. Field-testing such tools with the public has also improved their reliability<sup>244</sup>.

It is hypothesised that formatting the look and presentation of the LRBCS study questionnaire will ensure that it is developed in a way that it is both appropriate and appealing to the target population. Researchers of the LRBCS concluded that PPI would be an important and particle method for assessing the acceptability and accessibility of the online LRSQ. Furthermore it was deemed essential to develop the LRBCS with the prospective study population.

## 5.2.3 Method

### 5.2.3.1 Development

A literature search identified elements of the format and design that impact the attitudes of participants towards study questionnaires. This may affect initial response rates, likelihood to complete the questionnaire and loss to follow-up<sup>229, 249, 254, 261</sup>. Table 5.1 concludes important elements that were considered when designing the questionnaire. The focus of this PPI work was to address the design, overall appearance and delivery of the questionnaire to the LRBCS population of interest.

**Table 5 1: Factors that Optimise Questionnaire Design**

Category	Area	Example
<b>Layout</b>	Order of questions	General questions need to precede specific questions (minimize conditioning), group similar questions together <sup>249, 254</sup> .
	Demographic Questions	Need to be placed at end of questionnaire (viewed as tedious) <sup>251-253</sup> .
<b>Content</b>	General	Similar questions must be grouped together <sup>249, 254</sup> .
	Language	Avoid vague terms/jargon and explain abbreviations <sup>250</sup> .
	Introduction	Outline purposes, justification and how the information will be used <sup>247</sup> .
<b>Design</b>	Font	Imperative that the font chosen is clear and legible as readability is important <sup>247, 250, 254</sup> .
	Page density	Less pages does not necessarily make questionnaire seem shorter, and a more dense questionnaire may be viewed as tedious <sup>247, 248</sup> .
	Colour	Enhances the questionnaire's overall appearance <sup>254</sup> .
	Images	Recognisable graphs and logos remind participants of research's purpose <sup>247</sup> .
<b>Appearance</b>		

### **5.2.3.2 Research Material**

Key variables identified from literature enabled researchers to develop interview questions and prototypes of the questionnaires using different design elements and format. Important variables identified include layout, density of questions and information, question order, use of colours, backgrounds, images and logos. In addition to font size and colour. These variables have been shown to affect participants' attitude toward the questionnaire and response rates.

This PPI study would aim to appraise five domains; accessibility, density, font size, use of themes, images logos and background use (summarised in Table 5.2). In order to do this, prototypes of the questionnaire were developed and prepared, embracing import features of questionnaire design identified from literature (see appendix 4, figure 8.5). These prototypes were categorised into five short questions, each assessing the key domains identified. The prototypes provide visual prompts and enable interviewees to quickly identify their preferred answer. Between three to four prototypes were developed for each domain assessed (see appendix 4, figure 8.7). The interviewees selected would meet the same inclusion criteria as the LRBCS (see protocol in Chapter 2).



**Table 5 2: Summary of Prototype Domains and Questions**

Domain	Definition	Prototype	
		Label	Options
Accessibility	Are participants able to easily access and complete the questionnaire	Paper	-
		Personal computer	Laptop/Desktop Computer
		Tablet	-
		Smartphone	-
Density	Volume of information displayed on each page including the spacing between questions	1	Low – one question per screen and approximately 3 lines of text
		2	Medium – similar questions grouped together, approximately 6 lines of text
		3	High– many questions and approximately 14 lines of text
Background	Impact of colours in which the questions are set	1	No colour
		2a	Coloured font only
		2b	Subtle colour
		3	Mainly colour
Themes, Images and Logo	Use of images, non-verbal communication, background and colour	1	Image of children holding hands along the footer
		2a	Plain background behind text with coloured vertical strips either side of the slide
		2b	Colourful pencils along the footer and a header in a typeface of child-like writing
		3	Very colourful and had a child-style illustration in the background
Font Size	Most appropriate size and style of font	1	Arial Size 16 Font
		2	Arial Size 12 Font
		3	Arial Size 20 Font

### 5.2.3.3 Delivery

Post-natal mothers that met the LRBCS inclusion criteria (see LRBCS protocol in Chapter 2) were approached at the LWH for individual interviews regarding the questionnaire. Initially, 20 mothers were approached on the 17<sup>th</sup> July 2012. Any feedback given by the infants' father was acknowledged but feedback from mothers took priority. Verbal consent was obtained and eligibility for the LRBCS was confirmed.

During the interview, mothers were shown standardised examples of specific presentations of the LRSQ and were asked to indicate their preference from three options and also given the opportunity to express their views and any concerns with the interviewers throughout the process. Interviews were conducted in a neutral manner, avoiding the use of emotive language that may produce bias. The interviews were conducted in a flexible manner allowing mothers as much time as needed to observe the examples, give feedback and ask any questions.

After reviewing the prototypes, mothers were asked if they would like to provide further comments or indicate any additional design, which were noted. Researchers also ask mothers to describe their overall perception of the prototypes, and if any factors relating to the format of online questionnaires might affect their likelihood to respond. To ensure data was consistent and to minimise bias, responses were recorded separately by both researchers, then discussed and agreed to ensure that there were not incongruity of the results.

## 5.2.4 Results

In total, 20 postnatal mothers that met the inclusion criteria for the LRBCS were approached and consented for interview. To minimise bias, two researchers recorded results separately. Additional comments were also summarised.

### 5.2.4.1 Accessibility

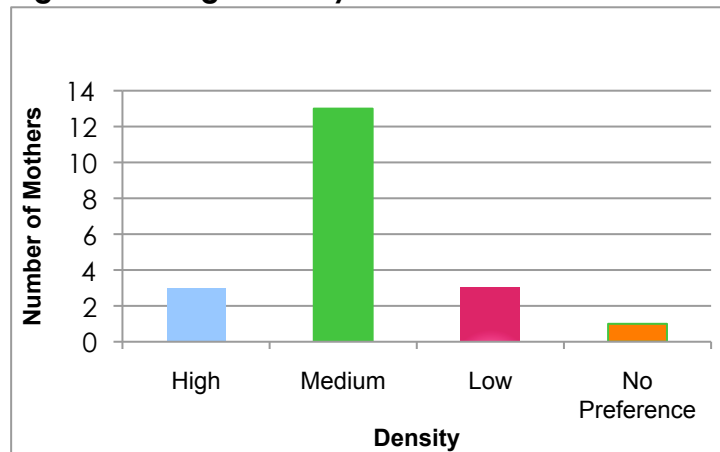
Accessibility to computers and methods of connecting to the Internet is an important factor to determine, as the LRBCS offers an online version of the questionnaire. It is also particularly important to ascertain as limited accessibility may lead to selection bias, affecting results from the online questionnaire<sup>227, 235</sup>.

Of the 20 mothers interviewed, the majority preferred to access the Internet using a laptop or desktop computer (n=13). All mothers had access to their preferred method of completion. Interestingly, none of the mothers interviewed, preferred to receive a postal version of the questionnaire. Of the 20 mothers interviewed, 19 mothers had access to a personal computer. Although 25% of the mothers (n=5) preferred to access the questionnaire via a smart phone, they considered this mode to be complex. Those who chose this option did so as they believed it to be less time consuming and that it is available at 'any place' at 'any time'.

#### 5.2.4.2 Page Density

This was categorised into three options; high, medium and low (summarised in Table 5.2). Significantly more mothers (n=13) preferred the medium density pages, which reflects results from

Figure 5.2: Page Density Preferences

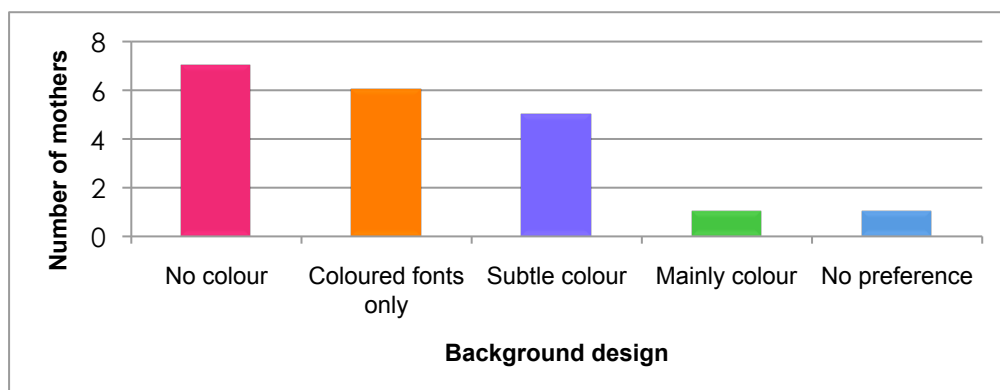


previous literature (Figure 5.2). This prototype was perceived to be the easiest to complete without being overwhelming. Low-density questionnaires were perceived as frustrating and endless. Contrastingly, high-density questionnaires discourage participants from completing the questionnaire.

#### 5.2.4.3 Background Design

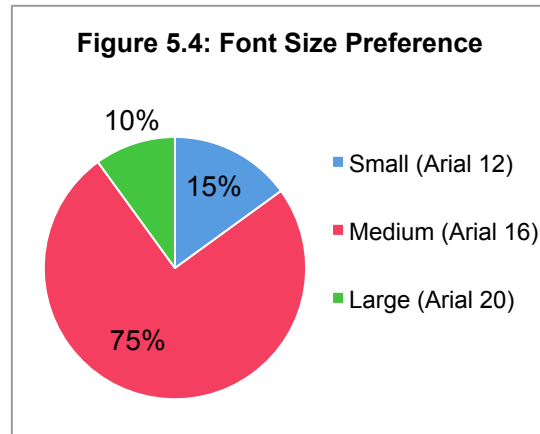
Four slides with varying background designs were created using a sample section of the questionnaire (options are summarised in Figure 5.3). Overall preference was for an uncoloured, plain background (n=7). However, results were close, six mothers preferred a plain background with subtly coloured fonts, while five indicated they would like some form of colour. Participants found this the most difficult to answer and many hesitated before indicating their overall preference.

Figure 5 3: Background Design Preferences



#### 5.2.4.4 Font Size

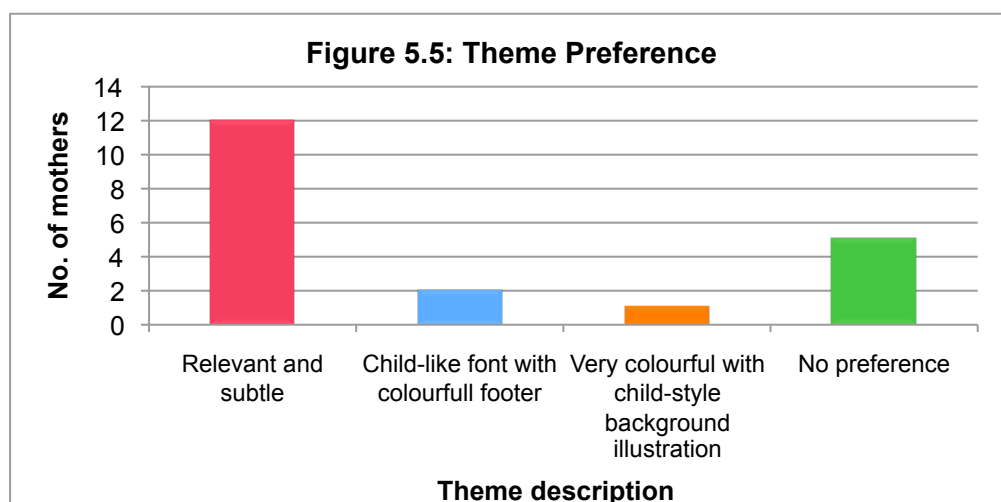
The size of the font affects the readability of the questionnaire<sup>262</sup>. Examples of small, medium and large fonts were given using sample slides of the questionnaire. The vast majority of mothers preferred the medium sized font (n=15)



(Figure 5.4). This font size corresponded to a size 16 Arial fonts. Three mothers preferred the smaller font size, while two preferred the larger font. The sizes correspond to size 12 and 20 Arial, respectively. However many mothers indicated that the font size was dependant on the screen size for an online questionnaire, so size is relative and other factors must be taken into account.

#### 5.2.4.5 Themes, Images and Logos

The final area investigated was the use of themes, images and logos. Literature recommends the use of relevant and friendly images and theme's appropriate for the questionnaire and cohort of interest.<sup>247</sup>. The majority of the mothers (n=13) indicated a preference for the slide with pictures of colourful children along the base (Figure 5.5). Five mothers indicated no preference although they would prefer minimal images.



#### 5.2.4.6 Additional Findings

Mothers were keen to be involved with the development of the questionnaire and were eager to provide feedback (Figure 5.6 below).

##### **Figure 5.6: Summary of additional feedback from Mothers**

- Ensure that there is enough information provided about the reason for the study.
- Images must be used efficiently –simple, relevant images can promote response, but too much can be distracting.
- Keep the appearance, simple, professional and important.
- Keep the overall questionnaire and individual questions ‘short and sweet’.
- Fewer ‘white space questions’ and include as few options as possible.
- Provide an estimate of completion time at the start of the questionnaire.
- Small incentives will make parents more likely to complete questionnaires.

#### 5.2.5 Discussion

This PPI work has been invaluable for developing a practical, accessible and appealing web-based questionnaire for use in the LRBCS. Results deduced from the responses of mothers to the prototypes will be applied to further develop the appearance of the questionnaire. This allows researchers to maximise response and attrition by designing a tool that appeals to the target population. Accessibility to the Internet was not an issue for any of the participants interviewed. Of the 20 mothers interviewed, all had access to the Internet and none said they would prefer to complete a paper version of the questionnaire.

Results clearly indicated that personal computers were favoured above other devices such as tablets or Smartphone's (65% in comparison to 25% and 10%). The particularly remarkable result that 100% of participants' would prefer to complete an online version not only highlights the increasing popularity and use of the Internet with regards to data collection, but also supports the decision to conduct the LRBCS online. A quarter of the cohort interviewed would prefer to complete the questionnaire on their smart phone. Therefore it would be reasonable to consider developing a mobile phone application version of the questionnaire to promote usability and accessibility. Current technology supports the development of such applications, although this may incur significant costs. Failing this, the survey software used must be compatible on smart phones so that the questionnaire may be completed using this method.

Trends with regards to font size, page density and background showed the majority of participants chose the intermediate option, which reflects results of previous studies. This may be as a result of participants answering way that is perceived as socially acceptable, or preferred by the researcher. This must be considered when interpreting the study's results particularly the majority of questions provided three possible answers. However both researchers felt that the majority of participants gave honest answers.

The questionnaire design will reflect the PPI preferences. Results justify the use of relevant, coloured images, in small quantities (60% of participants). Therefore the addition of colourful children will be added to the footer of the questionnaire slides. Results strongly support the use of a neutral background to questionnaire (35% participants), so in the design of the LRBCS questionnaire will reflect this to reduce distraction. Page density will be carefully considered, particularly as high density pages reportedly intimidate and confuse participants, whereas a low page density frustrates and confusing potential participants (see Table 5.2). Medium density was preferred which consisted of groups of similar questions per screen that included six lines of text.

### 5.2.6 Conclusion

Results of this study highlight the value and importance of involving patients and the public when designing and developing research tools and strategies. Results have provided a valuable insight into the importance of considering the design of research tools during qualitative research in aiding response rates, attrition and the overall reaction to the study.

Feedback received from mothers enable the researchers to tailor the both the study and questionnaire to meet the specific needs to of the population of interest. This will enable the research team to design a tool that not only appeals to this population but also maximises both recruitment and response rates. Evidence from this study suggests the final design of the questionnaire will have minimal use of patters and colours, medium sized font with modest, simple clean images.

### 5.2.7 Limitations

Numerous limitations must be taken into account, particularly when interpreting the results of this study. It is important to consider that researchers involved with the LRBCS conducted the interviews. This may have introduced some elements of observer bias both during data collection and interpretation of feedback given by parents. To try to minimise this bias, researchers collected data separately before collaborating results. This bias could have been further minimised by recording interviews, however this incurs ethical considerations. During interviews parents stated an overall preference for each domain, however a ranking system would have provided more consistent results for statistical analysis. Results would be more reliable and accurate had PPI taken place using a larger sample size, over a longer time period. In addition these results may not be representative of the whole population as only the LRBCS target population were included.



## 5.3 Feasibility: Adobe FormsCentral vs SelectSurvey.NET

### 5.3.1 Aim

To assess the feasibility, usability and readability of the online LRSQ, using both Adobe® Forms Central (AFC) and SelectSurvey.NET software (SS).

### 5.3.2 Introduction

Feasibility testing is imperative for the success of studies. A feasibility study may be defined as a preliminary study to determine a project's viability.

They are used to estimate important parameters needed to design the main study. In this particular case, a feasibility study is being conducted in order to aid the design and development of the LRBCS questionnaire.

Assessment of previous software methods for questionnaire delivery identified two potential survey software options for use in the LRBCS.

These include SS and AFC software was concluded to be the two most practical measures to design and carry out the questionnaire survey. The research team concluded that feasibility testing at the LWH would be the best method to ascertain the most effective survey software.

### 5.3.3 Method

#### 5.3.3.1 Design

Online versions of the initial mailing LRSQ questionnaire were created with identical questions and wording using both AFC and SS software. Members of the research team and colleagues tested both questionnaires before implementing a feasibility study to confirm the usability of the online questionnaires. In order to assess the delivery of the questionnaire, both drop down and matrix style questions were included in the questionnaires trialled.

The AFC questionnaire design included drop down options, while the SS questionnaire include some matrix-style options. This format was chosen due to the issue that the SS software did not provide the adequate facilities to construct questions with drop down style questions that were presented in the prototype version of the questionnaire developed from PPI testing (see appendix 4, figure 8.6).

Interview questions were standardised and predetermined before mothers were approached (See Appendix, figure 8.7). Questions were divided into those asked before, during and after mothers completed the questionnaire. Questions covered aspects such as aesthetics, perceived readability, comprehensiveness, usability, length, overall rating (/10), and overall preference. Mothers were also given the opportunity to provide further feedback and raise any concerns that they had with both questionnaires.

#### **5.3.3.2 Delivery**

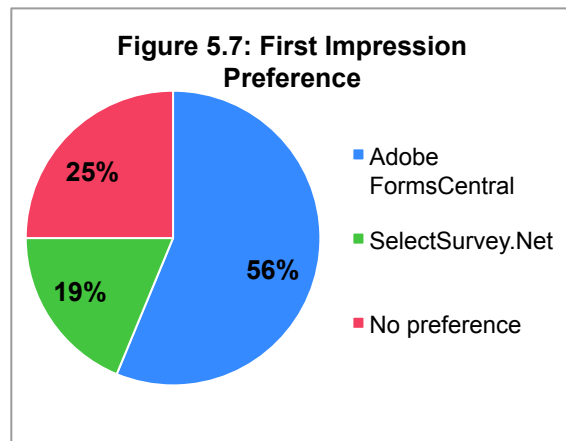
A total of 16 post-natal mothers that met the LRBCS inclusion criteria (see LRBCS protocol in appendix) were approached on the maternity wards at the LWH, on the 17<sup>th</sup> of October 2012. Mothers were asked to complete both versions of the complete online questionnaire in their own time. This was done using a portable tablet, in the presence of two researchers. The order in which the two different versions were shown to participants was alternated between mothers to minimise bias. Before, during and after completing the questionnaires, mothers were interviewed about several aspects of the two questionnaires. After completing each individual questionnaire, mothers were asked to give each questionnaire a score out of ten. At the end of the interview mothers were asked to indicate their overall preference and also given the opportunity to provide additional feedback for both versions of the questionnaire if they so wished.

### 5.3.4 Results

In total, 16 postnatal mothers that met the inclusion criteria for the LRBCS were approached and consented for interview. Mothers completed two versions complete versions of the questionnaire created using AFC and SS software. To minimise bias, two researchers alternated which questionnaires were completed first and additional feedback for both software options was summarised.

#### 5.3.4.1 First Impressions

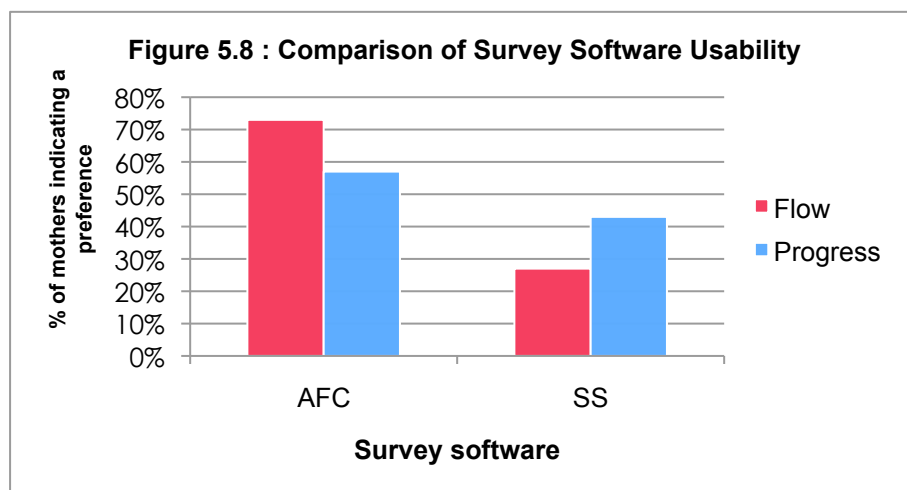
Notably, on first impressions, the majority of mothers preferred AFC questionnaire (56%, n=9) (Figure 5.7). Of the 16 mothers who participated, 15 indicated a preference towards an online version of the questionnaire.



This further supports the preferred delivery results from the study.

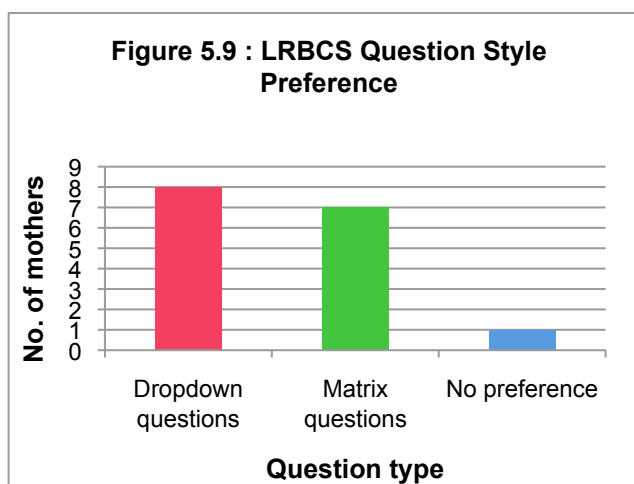
#### 5.3.4.2 Understanding, Length and Flow of Questionnaire

All of the mothers questioned, understood each and every question of the LRBCS questionnaire. The majority of the mothers interviewed also deemed the length of the questionnaire acceptable (n=14). Two mothers commented that AFC seemed quicker to complete while another commented that select seemed quicker to complete. Of those who reported a preference, AFC was clearly the preferred survey software (Figure 5.8).



#### 5.3.4.3 Questionnaire design

The format of questions has been shown to improve response rates and reduce attrition<sup>247, 248</sup>. Researchers were unsure as how was best to present the LRSQ questions and concluded that this would be best concluded by interviewing potential participants. Mothers who preferred the matrix style questions did so as they were perceived as quicker and easier to read.



However, the reliability of data received using this method is questionable, particularly as some interviewees admitted that they did not read the questions completely as they were able to quickly select the check boxes. There were no negative comments with regards to the preferred dropdown style questions (Figure 5.9).

#### 5.3.4.4 QR Code

Although 60% of mothers recognised QR codes, the majority of mother implied that they would be unlikely to use the sign-up QR code and preferred the postcard method of recruitment. Actual QR code is shown in figure 5.10.

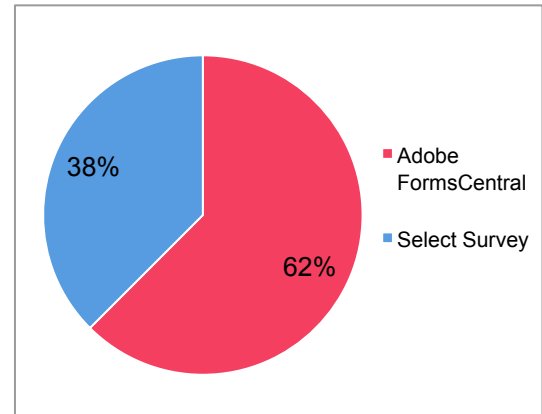
**Figure 5.10: QR Sign-Up Code for the LRBCS**



#### 5.3.4.5 Overall Software Preference

The results of this small feasibility study are illustrated in figure 5.11. Of the 16 women who participated, 62.5% (n=10) indicated that the overall preference was for AFC. Average overall score (/10) was 8.36 and 7.8 for AFC and SS, respectively.

Figure 5 11: Overall Software Preference



#### 5.3.4.6 Additional Feedback

There was largely a positive response to the feasibility testing (Figure 5.12). Mothers were very willing to provide feedback about the usability, format, and design of the questionnaire in addition to expressing their views on the survey software. This valuable feedback resulted in changes to both the questionnaire wording and format in addition to a few minor amendments to the study itself.

Figure 5.12: Additional Feedback from Mothers

- Mothers felt their responses weren't needed if their baby was symptomless.
- Some mothers felt happier to take part in the study after reading more information.
- Many mothers did not notice the 'read more information' option.
- Mothers liked the descriptions below the questions as opposed to the help buttons, particularly for wheeze and rattly chest definitions.
- Positive feedback for the colourful children at base of questionnaire-indicated topic and brightened questionnaire design.
- Mother's felt more reassured and more likely to participate having seen the LWH FT logo.
- Mothers wanted to understand the benefit of the study and what it is hoping to achieve – happy if other children would benefit and not their own child.
- Mothers prefer not to receive the postcard with the bounty pack –too many leaflets so many unread.
- QR codes recognised by the majority of mums but none said they would be likely to use them.

## 5.4 Discussion

The aims of this study were to test the feasibility and acceptability of the web-based LRBCS questionnaire, and to explore any differences between two questionnaires developed by different survey software options. Results from this small feasibility study provided researchers with necessary results to choose the most appropriate questionnaire software and to develop an appealing and practical questionnaire. They also concluded that the finalised questionnaire is a feasible and acceptable tool for use in the prospective LRBCS population.

A clear overall preference was found for AFC software over SS software, with 62.5% (n=10) of mothers preferring the former. In addition, the 56% of mothers also preferred AFC on first impression, although 25% of mothers had no preference. Encouragingly, 100% of mothers understood each question and were able to complete the questionnaire with minimal direction, maintaining that the questionnaire is suitable and comprehensible.

Previous studies have emphasised the importance of questionnaire design for participation, response rates and attrition, particularly with regards to the format of questions<sup>247-249, 261</sup>. The format of the online questionnaire also affects its perceived length, in addition to the time taken for completion. Dropdown and matrix questions were identified as the most appropriate method for presenting the LRSQ questions. Feasibility testing demonstrated that dropdown style questions were marginally more popular than matrix style questions. Concerns over the validity of data collected using matrix style questions prompted researchers to proceed with the dropdown question design<sup>232</sup>. Results from previous studies and feedback from mothers suggested that matrix style questions might compromise data collection as answers may be given quickly, preventing the need for respondents to read the questionnaire properly.

Progression through the questionnaire and flow are also important factors to consider. Of the mothers who indicated a preference towards a particular survey software, the majority expressed a preference towards the AFC questionnaire (73% flow and 52% progress). Mothers also highlighted the clear, percentage progress bar on AFC as a particularly useful feature and also felt that the AFC questionnaire was quicker to complete. Results from this study emphasise the importance of skip logic that obviates need to complete irrelevant questions and reduces the time needed to complete the questionnaire, an important factor with regards to response rates. AFC enables skip logic preventing unnecessary questions from being asked unless the 'trigger' question selected. This means only relevant questions are asked thus reducing the overall time taken to complete the questionnaire, improving flow through the questionnaire.

AFC questionnaires are able to provide "help" buttons, headers and footers to give extra information to guide participants through the questionnaire without cluttering the page. However these must be used with caution as some mothers preferred help text to appear directly below the question. During interviews it must be noted that mothers who appeared more computer literate were more comfortable using the 'help' buttons. It is important to make the questionnaires as accessible as possible and in a format that appeals to the cohort of interest.

Feedback from mothers during interviews was used to further develop the questionnaire following the previous PPI work. This additional feedback prompted researchers to amend the phrasing of the demographic and exposure questions. The LRSQ questions were not edited, as these have been pre-validated in this particular cohort. These small, but necessary revisions are listed in the box below (figure 5.13).

#### **Figure 5.13: Revisions to Demographic and Exposure Questions**

- Mothers felt their responses weren't needed if their baby was symptomless.
- Some mothers felt happier to take part in the study after reading more information.
- Many mothers did not notice the 'read more information' option at the beginning of the questionnaire.
- Mothers liked the descriptions below the questions as opposed to the help buttons, particularly for wheeze and rattly chest definitions.
- The term 'child' confused mothers and felt questionnaires should be changed to reflect the age of the child of interest.
- Confusion over the asthma/allergy question – need to clarify that this is regarding a 1<sup>st</sup> degree relative only.
- Clarify DOB question is child's DOB not mothers.
- The 'save' button confused mothers so was subsequently removed
- Breastfeeding question was clarified to include expressed milk.
- Unsubscribe button must clarify that this is only selected if participants do not want to take part in the study
- Smoking question was edited- both now refer to smoking anywhere
- Clarify difference between smoking questions –one during pregnancy and the other is at any time.
- Question asking for 'mobile telephone number' has been changed to 'main telephone number'
- Drop down style questions decided for the LRSQ section of the

Results regarding QR code usage were not encouraging. Although 60% of mothers recognised QR codes and were aware of their use, they would be unlikely to use the codes to sign up. However, considering the ever-developing field of technology, this method will be used alongside personal recruitment, rather than replacing it. Study postcards and posters will include the sign-up QR codes, with instructions on their use. This method of recruitment may then be assessed alongside personal recruitment.



Additional revisions to the study and other material given to mothers were made following the feedback listed below (figure 5.14). Mothers felt that it was particularly important for recruitment material to clearly explain the study's purpose, both on the recruitment postcards and questionnaire. The colourful children at the footer were appealing to the majority of mothers interviewed so will be included on more study documentation. One issue raised was that mothers were unsure that their babies might be included despite being symptomless. This prompted researchers to clarify in the initial information presented to mothers, that all babies may be included in the study regardless of whether they experience respiratory symptoms or not.

**Figure 5.14: Additional Revisions Following the Feasibility Study**

- Clearly explain what the study is hoping to achieve on postcard and questionnaire.
- Include colourful children in more study documents.
- Clarify on all documents and during recruitment that all babies are being recruited and included into the study, not simply those with symptoms.

## 5.5 Conclusion

This feasibility study concluded that the majority of participants preferred AFC to SS (n=10 in comparison to n=6, respectively). This supports the decision to conduct the online LRBCS, particularly using AFC survey software. The questionnaire design has been further edited following feedback from mothers to ensure it appeals to the population of interest and the final version of the initial version may be accessed at <http://goo.gl/mm565>. QR code recruitment will be used to potentially facilitate recruitment but will certainly not replace the postcard recruitment method.

## 5.6 Limitations

Limitations of this small feasibility study must be considered when appraising the quality of data. Observer bias must be taken into account with these results as researchers involved with the LRBCS conducted the interviews. This may have introduced an element of observer bias in the collection and interpretation of the information provided by parents.

However, this could be an advantage in some respects as researchers were able to take every bit of feedback into account. Results of interviews are subjective and may be interpreted differently. All mothers completed alternated versions of each questionnaire. However this may have affected mothers overall preference. This study targeted a specific population group, thus inferences made may not represent the whole population.

Furthermore, results may have been more reliable and of more significance with a larger sample size.

## 5.7 LRBCS: Estimated Cost

The financial burden of birth cohort studies may easily be underestimated<sup>83</sup>. The cost implications of this study have become more substantial as the study design has progressed. Literature has implied that web-based studies have a smaller financial burden<sup>183, 184, 197</sup>. This has appears to be true for the LRBCS. Despite the cost of the survey software, mailing credits and recruitment postcards, the main burden for this study financially has been the postal side. The cost of postal stamps alone overshadows the cost of the technology and recruitment postcards. This is before the cost of printing and stationary has even been taken into account.

All aspects that impact the study financially were thoroughly researched before being considered. Feasibility testing concluded that AFC would be the most appropriate survey software. MailChimp® was identified as being the most suitable automated service that complied with the study's requirements. After researching numerous printing facilities for the cheapest option that fit the study's specifications, Saxoprint was recognised as being the most appropriate choice. Postcards must be A5 size to ensure that they are legible. Colourful postcards will encourage interest and improve the aesthetic appeal, as well as ensuring that continuity between the stationary and the online forms. A matt or silk finish will guarantee a professional finish, while ensuring participants are able to complete the postcards with a pen. Postcards are cheaper if printed in bulk. A bulk order of 10,000 is needed in order to meet the maximum recruitment strategy.

The start up cost of the study has been calculated in order to demonstrate the initial start up funding required (see Table 5.3). The study's total cost has been calculated for a period of 6 years, which is the minimum expected duration of the LRBCS (see Table 5.4). Recruitment will take place during the first year of the study, and children will be followed up biannually until the last child to be recruited has reached his or her fifth birthday.

**Table 5.3: LRBCS Start-up Cost**

Resource	Provider	Specifications	Quantity/ Duration	Cost	Total
Survey Software Subscription	Adobe FormsCentral	Annual subscription	1 year	£105.39/year	£105.39
Email Credits	MailChimp®	Pay-as-you-go Email Credits	25,000 credits	£156.73	£156.73
Postcards (A5)	Saxoprint	10,000 postcards A5, double-sided colour 250gsm, matt finish	10,000	£223.93	£223.93
Post-boxes	UK Point of Sale	white post-boxes that include postal holder	4 boxes	£20	£80
				<b>Total</b>	<b>£566.05</b>

**Table 5.4: LRBCS Total Cost**

Resource	Provider	Specifications	Quantity/ Duration	Cost	Total
Adobe Forms Central Subscription	Adobe FormsCentral	Annual subscription	6 years	£105.39/year	£626.34
MailChimp® Email Credits	MailChimp®	Pay-as-you-go Email Credits	225,000	0.0003p/credit	£783.65
Postcards (A5)	Saxoprint	10,000 postcards A5, double-sided colour 250gsm, matt finish	10,000 x 6 years	£223.93	£1,343.58
Post-boxes	UK Point of Sale	White post-boxes that include postal holder	4	£20	£80.00
Postal Stamps	Royal Mail	2nd Class Stamps	250 stamps x 11 rolls	£250	£2,750.00
				<b>Total</b>	<b>£5,583.57</b>

Before commencing recruitment, financial support was required to fund the study. An application for funding (see appendix five, figure 8.8) was submitted to the study's lead sponsor, the University of Liverpool, which was kindly accepted. The friends and family of Isabella have kindly provided additional financial support, many of which work for the North West Ambulance Trust, who gave a generous donation of £1,000.

## 5.8 Conclusion

Feasibility studies have been identified as constructive means to improve recruitment, response rates, attrition and overall reaction studies study. Using PPI during feasibility testing enabled the research team to tailor the design and appearance of the questionnaire to appeal to the target population, while maintaining usability. AFC was identified as the most appropriate software option and measures have been taken to finance this effective survey software. Feasibility testing also evaluated the online version of the questionnaire in terms of accessibility and demand, concluding that it is a viable method for data collection.

## 6 Recruitment Pilot

### 6.1 Background

The recruitment strategy changed over the development of the study's protocol. The original plan, was to integrate recruitment into routine clinical practice. This would involve Senior House Officers and Midwives recruiting mothers during initial baby checks prior to discharge from the LWH. However, it soon became clear that this would not be a practical and dependable method. An effective recruitment plan was clearly imperative for the success of the study. After discussing the proposed method in depth with other members of the research team and the LWH's Local Collaborator, it was decided that the most viable and effective method would be for one member of the research team to personally meet new mothers and seek expressions of interest. This would be achieved by handing new mothers a postcard detailing an overview of the study and spaces on the same post card for completion of contact details. In order to develop an effective and feasible strategy to maximize contact with new mothers, a month pilot recruitment period was proposed which would enable the team to develop a site-specific recruitment plan alongside midwives and experienced paediatricians. Recruitment may be divided into two-stage process describe in figure 6.1.

**Figure 6.1: Description of the two-stage Recruitment Process**

**Stage 1: Expression of Interest** – this involves a member of the research team approaching post-natal mothers at the LWH, at which point mothers are asked to complete a recruitment postcard with their contact details, indicating an expression of interest in the study and consent to be contacted.

**Stage 2: Consent and Completion of the Initial Questionnaire** – 4 months after birth, mothers are emailed or posted the initial questionnaire which includes consent to take part in the study

### 6.1.1 Preparation

Prior to recruitment, a meeting was arranged with the site's Local Collaborator, Professor Ben Shaw and Senior Midwives in charge of post-natal wards. This was an opportunity to explain the method and aims of the LRBCS, to raise the study's profile and provide an opportunity for the study's recruiters to be introduced. In addition, it provided a chance for midwives to raise any issues or concerns prior to pilot recruitment. Midwives were each given a study pack containing the recruitment postcard, an A4 version of the recruitment poster, the LRBCS protocol and a document designed specifically for the midwives. The midwife's document detailed the study's methodology and recruitment strategy.

### 6.1.2 Administration

Before initiating recruitment, collaboration with the R&D Co-ordinator was required in order to obtain the necessary letter of access for each researcher planning to recruit at the LWH. A3 posters were given to Senior Midwives in charge of each postnatal ward and erected in areas of the ward where staff felt mothers were most likely to see them. In addition, post-boxes containing an A4 version of the poster and a slot for recruitment postcards were also deposited in each postnatal ward in an accessible location.



### 6.1.3 Plan

Members of the research team would personally recruit each mother from post-natal wards at the LWH. This method has shown to be the most effective in previous studies<sup>133</sup>. Single centre recruitment took place at the Liverpool Women's Hospital, with a maximum recruitment strategy employed in order to recruit as many babies as possible. Neonates were recruited from the neonatal unit prior to discharge. The neonatal department agreed to lead neonatal recruitment and the research team collected postcards monthly and monitored recruitment. Mothers and midwives were asked to deposit any stray postcards in the collection boxes situated on each post-natal ward. Postcards and posters (see appendix) include a sign-up QR code with instructions on use. Spare blank postcards were left next to each collection box.

## 6.2 Recruitment Pilot

In order to establish the most effective recruitment strategy, a pilot recruitment period was deployed for one month. New mothers were personally approach on the post-natal wards at the LWH. The aim of this pilot was to develop a feasible recruitment strategy and evaluate the most viable timetable for recruitment.

### 6.2.1 Method

The four-week pilot recruitment period began on the 28<sup>th</sup> of January 2013, continuing until the 24<sup>th</sup> of February. Before the pilot commenced, two members of the research team conducted three days of 'practise recruitment' in order to minimise the potential bias due to the inexperience of the recruitment team. A four-week plan that covered possible times to recruit was finalised by the research team (see table 6.1).

**Table 6.1: Pilot Recruitment Plan**

Week	Days	Times
1	Seven full days	9.30 – 4.30
2	Six mornings	9.30 – 12.30
3	Five days (Monday to Friday)	9.30 – 4.30
4	Alternative days (Mon/Weds/Fri/Sunday)	9.30 – 4.30

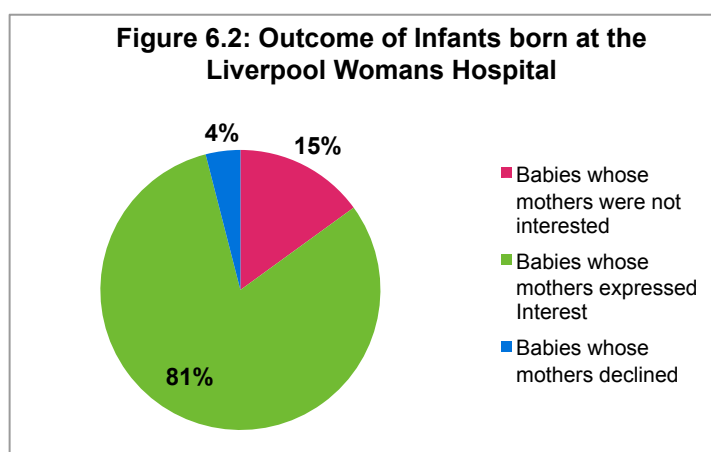
### 6.2.2 Results

In total, 334 infant's mothers expressed interest in the study during the pilot. The mothers of an additional 39 infant's mothers expressed interest over the initial three practice days. During the course of the four-week pilot, the research team approached 75% of post partum mothers resident within eligible postcodes. Of the eligible mothers approached by a member of the research team at the LWH, 82% completed postcards to indicate their interest in the study. Using infant discharge data that included postcodes, the research team was able to identify that 61% of eligible infants born at the LWH had an expression of interest postcard completed by their mothers. On average, the mothers of 80 infants expressed an interest in the study per week during pilot recruitment. Using the discharge data from the LWH it was only possible to identify infants with eligible postcodes and not those that would be excluded due to the inability of the parents to speak English or the complication of infants being taken into care. Therefore, table 6.2 may not show a complete reflection of mother's expression of interest.

**Table 6 2: Summary of Pilot Recruitment Results**

Pilot	Number of Infants		% Expressed Interest	Margin of error	Range (95% CI)
	Eligible	Expressed interest			
Full Five Days	121	68	56	±8.84	47.16%- 64.84%
Six Mornings	145	89	61	±7.94	53.06% to 68.94%
Alternate Days	132	76	58	±8.45	49.55% to 66.45%
Seven Full Days	140	101	72	±7.44	64.56% to 79.44%
Total	538	334	61	±4.12	56.88% to 65.12%

Expression of interest figures did not vary substantially during the pilot (see table 6.2). All ranges calculated using a 95% confidence interval overlap to a certain extent. Subsequently using the margin of error calculated it is impossible to conclude that one pilot week had a better outcome than another. The research team subsequently decided that the most feasible and viable recruitment strategy would include recruiting for a minimum of four mornings per week. This would include Mondays and Fridays as they were deemed the most important days to account for any losses over the weekend.



Of the mothers approached, 15% were not eligible either because they could not speak sufficient English, lived outside the L1-38 postcodes or for other reason such as infants were going into care (see figure 6.2). In total, 81% of all mothers approached by a member of the research team expressed interest whilst 95% of eligible mothers expressed interest. In addition, 78% of mothers indicated that they would like to receive the questionnaire by email while 22% expressed a preference for the paper version to be sent by post.

#### **6.2.2.1 Demographics**

Of the infants whose mothers expressed an interest in the study, 176 (49%) were male and 183 (51%) were female. This small difference in sex ratio is not significantly different to the expected sex ratio of live births described by the Office of National Statistics<sup>263</sup> (2008) ( $X^2=0.688$ ,  $p>0.5$ ).

During the pilot period, the mothers of three sets of twins expressed interest. Infants were recruited from the majority of the Liverpool postcodes L1-L38. Figure 6.3 (below) shows the proportion of mothers per Liverpool postcode that expressed interest in comparison to the proportion of mothers later giving consent and returning completed questionnaires by each Liverpool postcode.

**Figure 6.3: Proportion of Infants per Liverpool Postcode**

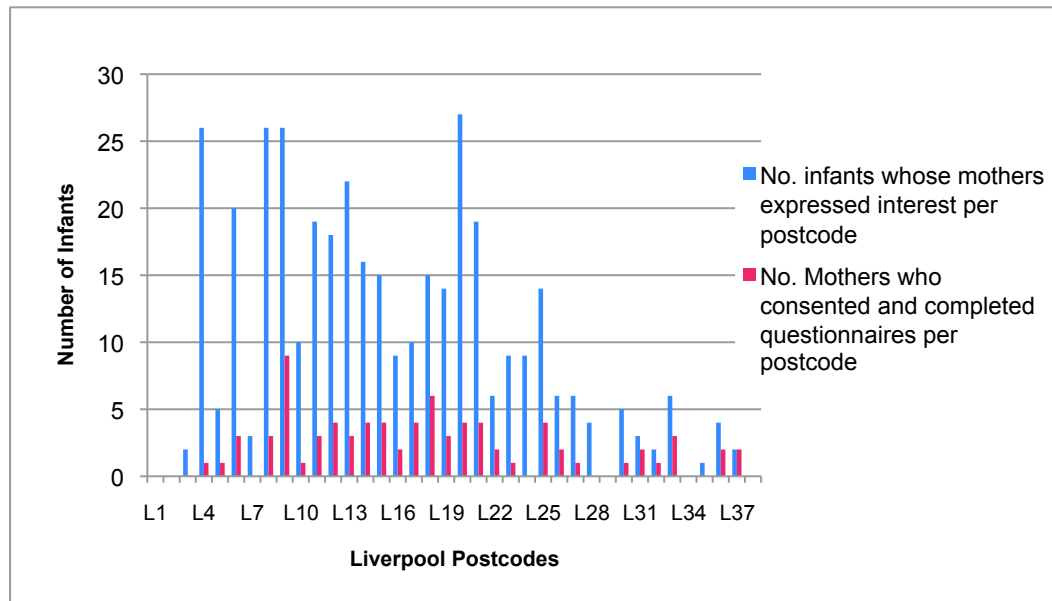


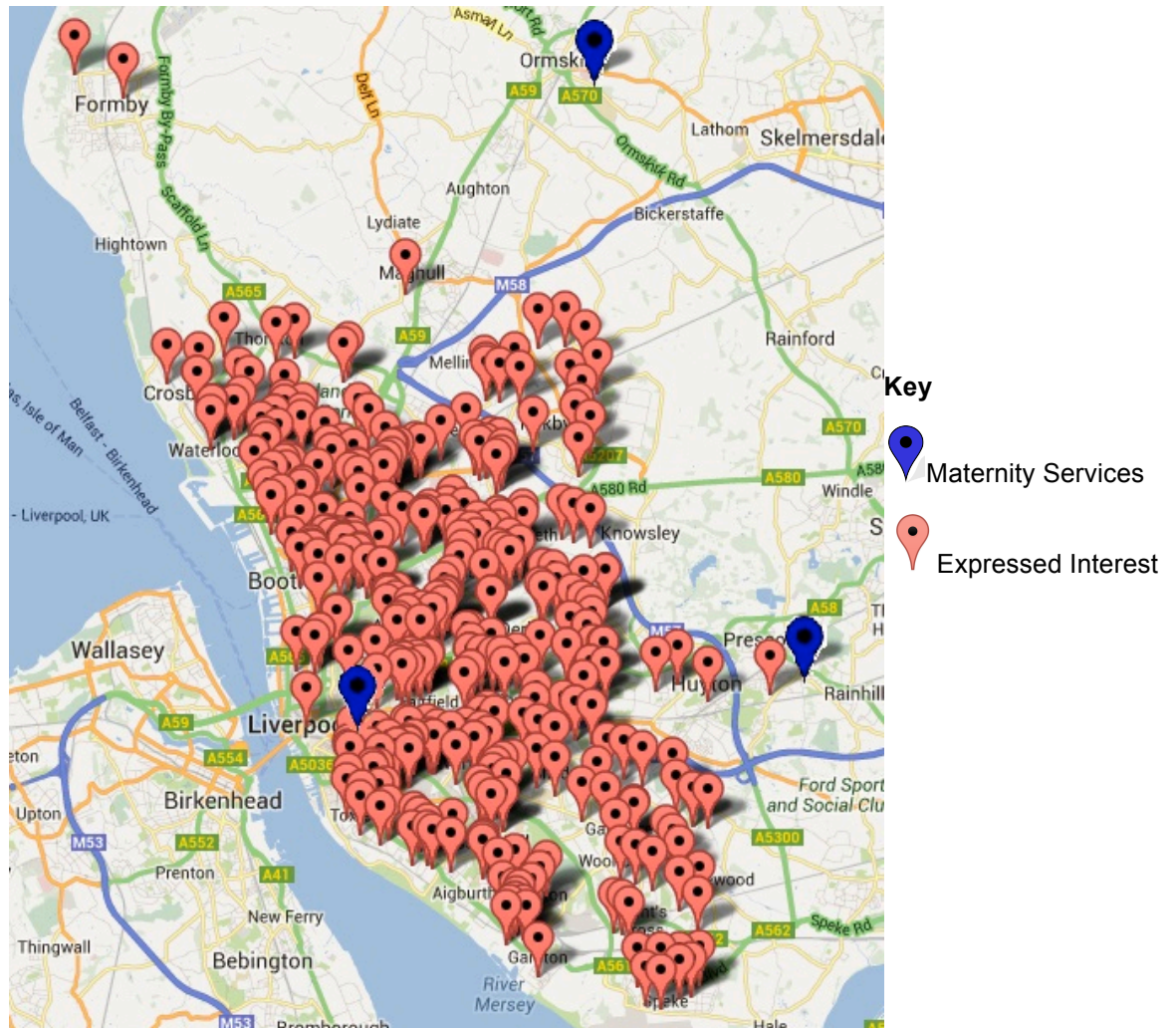
Figure 6.4 shows a map demonstrating the geographic representations of the mothers approached at the LWH, who expressed an interest in the study. The sparseness around the Southport and Ormskirk Hospital NHS Trust and St Helens and Knowsley NHS Trust may be accounted for by proximity to local maternity services offered at both Ormskirk and Whiston hospital, and maternal choice to deliver at these trusts.

This may result in poor geographic representation of these particular areas in the LRBCS cohort, and this should be determined in future analysis.

Ormskirk postcodes include L39 and L40, which are excluded from the study. However surrounding postcodes include L31 to L33 and L37.

Whiston is an L35 postcode with surrounding postcodes that include L26 to 28 and L34 to L36.

**Figure 6 4: Geographical Representation of Expressed Interest and Maternity Services**

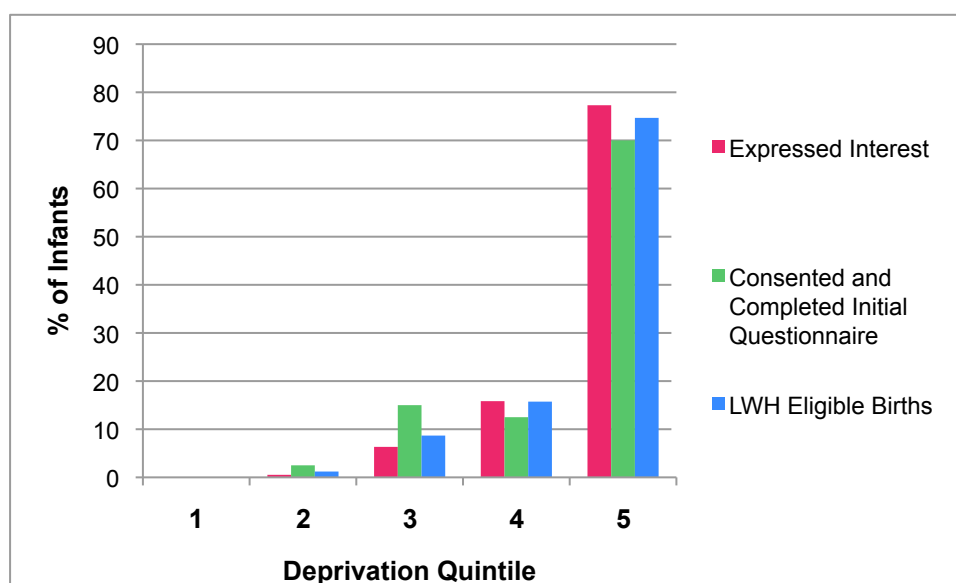


The relatively West and central blue pin represents the LWH while the subsequent blue pins represent Ormskirk (North) and Whiston (East) Hospitals (see Figure 6.4).

Preliminary analysis with regards to deprivation, demonstrates that the mothers expressing interest are representative of the mothers delivering at the LWH. The same can be said for the mothers giving consent and completing the initial questionnaires when their infants are 4 months old. No statistical difference was found between the proportions of infants in each IMD deprivation quintile whose mothers expressed an interest ( $n=379$ ) and mothers of all LWH births ( $n=553$ ) ( $X^2=2.234$ ,  $p>0.05$ ) (see calculation

matrix and table in appendix 5, figure 8.8 and table 8.9)<sup>264</sup>. No statistical difference was also found between the proportion of infants' mothers who consented and completed the initial questionnaire (n=80) and all LWH births ( $X^2=5.238$ ,  $p>0.5$ ). Furthermore, no statistical differences were found between all three groups ( $X^2=10.122$ ,  $p>0.05$ ). These are preliminary results with limited data, so further analysis is essential to determine the LRBCS cohort is truly representative of infants born at the LWH. The graph below (Figure 6.5) demonstrates that the proportion of infants recruited per quintile, in comparison to those whose mothers have consented and completed the initial questionnaire and the demographics of the infants born over the same time period at the LWH. It also highlights that the great majority of infants born in Liverpool and born into the most deprived quintile.

**Figure 6 5: Proportion of Infants by IMD Deprivation Quintile**



The table below portrays the ethnicity of the overall Liverpool population in comparison to infants recruited, whose mothers consented to take part in the study and completed the initial questionnaire 4 months after birth (table 6.3). No data was collected regarding ethnicity during the first stage of recruitment (expression of interest) so this could not be collaborated and contrasted. The Liverpool population is notably less diverse than the population of England with a predominantly white population<sup>265</sup>. This is reflected in the high percentage of mothers who consented and completed

the initial questionnaire reporting their infant as white (94%). At present the infants of mothers who returned the initial questionnaire does not appear truly representative of the ethnicity of Liverpool's population, particularly with regards to the Asian population. However these are preliminary figures so further analysis once more data becomes available.

**Table 6.3: Proportion of Infants per ethic group in comparison to the Liverpool baseline population<sup>265</sup>**

<b>Ethnic Group</b>	<b>Recruited Infants*</b>	<b>Liverpool Population<sup>265</sup></b>
White Total	94%	91%
White British	90%	86.30%
Other White	4%	4.70%
Mixed	3%	2.00%
Asian or Asian British	0%	3.00%
Black or Black British	1%	1.90%
Chinese or other ethnic group	1%	2.10%
Prefer not to say	1%	0%

\*Recruited Infants equate to those whose mothers consented to take part and completed the initial questionnaire.

### **6.2.2.2 Response Rates**

Of the 370 infants whose mothers expressed interest during the 'practice' and pilot, one mother declined to take part, after expressing an interest. One infant was identified through access to the NHS Personal Demographics Service as deceased, resulting in the infant's mother being removed from the study's contact list. From the remaining cohort, a total of 22% of mothers returned completed consent and questionnaires; 12% were postal responses in comparison to 88% online responses. Respondents were shown to be representative of the infants born at the LWH over that period, particularly with regards to those categorised into each deprivation quintile.



### 6.2.3 Conclusion

Results from the pilot and the experience of the recruiting research team enabled a plausible strategy to be developed. Recruitment would take place for four days per week. The majority of recruitment takes place in the morning but this would be left to the digression of the recruiter. Experience from pilot recruitment emphasised the importance of recruiting on a Monday, particularly if no recruitment took place over the weekend. Results from recruitment are reassuring with 82% of the eligible mothers approached expressing an interest in the study and 22% of these consenting to take part and completing the initial questionnaire.

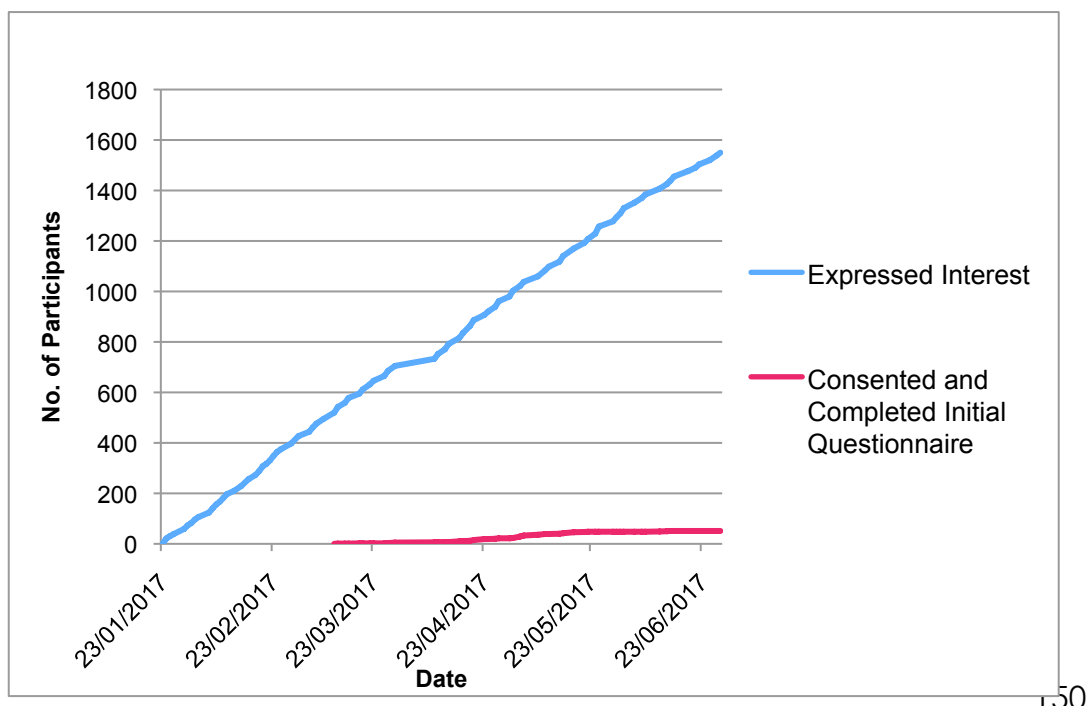
## 6.3 Final Recruitment Strategy

The recruitment strategy decided upon following the pilot took place over four days per week, usually Monday, Tuesday, Thursday and Friday. This was trialed for one week to reconfirm its viability and efficacy. A member of the research team successfully recruited a total of 83 infants over the course of four weekdays, these being Monday, Tuesday, Thursday and Friday. One day a week was set aside in order to accommodate the administrative burden of the cohort. This involved organising and sending postal questionnaires, validating postal addresses and checking missing details using the Alder Hey Children's Hospital database, MEDITECH© (Medical Information Technology Inc. Massachusetts USA). Other administrative activities included, sending in encrypted format the updated list of interested and recruited infants to an Alder Hey Information Officer to ensure no notice of death had been received by the NHS strategic Tracing authority, uploading participant's details to MailChimp®®® (The Rocket Science Group, Atlanta USA) and the LRBCS database, while checking mailing and survey software are working correctly and updating the LRBCS website.

## 6.4 Recruitment Results To Date

To date, the recruitment strategy appears very effective, with over 1,330 infants mothers, who delivered at LWH, expressing an interest (53% of eligible births) by the end of May 2013. Furthermore 166 from 618 deployed questionnaires were returned indicating that 27% of mothers have given consent and returned data four months later. Personal recruitment has proven to be the only viable option. Only one mother spontaneously completed a spare blank postcard placed by the information board. In addition, only one mother has used the QR link to the sign up to join the LRBCS. On average 73 babies are recruited per week and the majority are recruited when they are one day old. With regards to sex, 49.80 % of babies recruited are male while 50.1% of babies recruited are female. One set of triplets and 28 sets of twins have also been recruited. At least one baby has been recruited for each of the eligible postcodes, L1- L38. Below is a cumulative total graph demonstrating the expressions of interest and respondent to the initial questionnaire with on-line consent and completion of first questionnaire (Figure 6.6). The visible pause in numbers recruited is due to the recruitment team taking one week's annual leave over the Easter period.

**Figure 6.6: Cumulative Total for Expressed Interest and Consent**



## 6.5 Conclusion

Recruitment has been incredibly successful and congratulations must be made to the recruitment team, particularly Miss Bethan Griffith. Preliminary analysis has shown that the group of Mothers expressing an interest in the LRBCS study are representative of the Liverpool new mother and local population in terms of demographics. Further analysis is required when further data becomes available, particularly with regards to ethnicity and social deprivation. Recruitment will continue for a minimum of one year, up until the 27<sup>th</sup> January 2014. Depending on the continued success of recruitment this may continue as rolling recruitment for a further 4 years.

# 7 Discussion & Conclusion

## 7.1 Discussion

The design, development and initiation of the LRBCS have been described and discussed in this thesis. The development of the protocol in collaboration with preparation and application to NRES has been an iterative and incremental process. Collaboration with various organisations and trusts was an important part of the protocol development and particularly for the NRES application via IRAS. Application by proportionate review was a particularly successful process, avoiding the delay often incurred by a full ethical review. Members of the research team were not asked to attend the meeting but instead were available to answer any questions about the study by telephone.

The online aspect of the LRBCS is a crucial part of the study. Its development required an understanding of survey software; key features required, security issues and important design features. Once an understanding of these features was reached, the most appropriate survey software was selected, designed and developed. The use of automated emailing software was seen as imperative for the successful deployment of the questionnaire. A particularly challenging aspect was not only finding a suitable automated emailing service that allowed the research to schedule emails to send automatically, but also a system that did not incur significant financial cost.

Throughout the design and development phases, the Internet has proven itself as a valuable tool for research, particularly with regards to public health and epidemiology. The online questionnaire is quicker to complete and may be perceived as an easier method by some participants. However, previous literature gives mixed reports so researchers felt it was important to provide a paper option of the questionnaire. This provides an opportunity to compare the two methods. The pilot recruitment period was a valuable

asset while developing a feasible recruitment strategy. This provided an insight into the workings of the ward including the best time, method and approach to recruitment. It also demonstrated that of the methods used, personal recruitment is the best option. Only one mother completed and returned a recruitment postcard herself and in addition only one mother was recruited via the QR code.

The LRBCS will be an invaluable asset to the study of the Liverpool preschool respiratory epidemiology. It enables the research team to map parent reported respiratory symptoms in a population-based study of children from birth until the age of five. In addition the study data will enable the research team to describe how the respiratory symptoms of preschool children change over time, and environmental or social factors that make them more or less likely to occur, including to their effect on the child and their family. This is a unique respiratory birth cohort study in that results will allow the impact of children's respiratory symptoms upon the child and the child's family.

Liverpool is an area that continues to experience persistently high levels of deprivation. Figures from 2010 show that Liverpool remains ranked as the most deprived local authority area in England, a position unchanged from the 2004 and 2007 Indices<sup>146</sup>. These consistently high levels of deprivation make the city an ideal place to explore its impact upon the respiratory health of Liverpool children. Historically, Liverpool is an established site for exploring respiratory symptoms<sup>138</sup>. Numerous papers have been published, not only with regards to deprivation but also concerning to respiratory symptoms, deprivation, tobacco smoking, bronchiolitis, and asthma<sup>66, 140, 266-268</sup>.

This birth cohort study will provide a wealth of data, not only adding to existing knowledge but will also create a valuable basis for future research. Demographic details such as postcodes, maternal level of education, birth weight, gestation, age, sex and ethnicity of the child will be compared to not only respiratory symptoms but the burden of these symptoms on family life

in addition to reported co-morbidities, family history of atopic conditions and breastfeeding. In addition, important exposures such as, nursery attendance, other siblings in the household, children sharing a room, maternal smoking during pregnancy, smoking habits of any member of the household and chronic co-morbidities will be compared to parental reported respiratory symptoms.

The LRBCS will allow researchers to establishing associations between variables. One area of focus is identifying casual mechanisms linking social deprivation to respiratory disease. A number of social deprivation factors have been shown as possible casual mechanisms affecting a population's health and may subsequently affect respiratory health<sup>269</sup>. Social deprivation determinants of population health include income and social status, social support networks, education, employment and working conditions, physical environments, personal health practices and coping skills, healthy child development, prenatal and early childhood experiences and health services<sup>269</sup>. The design of a birth cohort study allows researchers to measure casual mechanisms and time-sequences as to how respiratory symptoms develop. Cross sectional studies are able to assess association but are unable to determine causality as the exposure and outcome are measured at the same time. Following the LRBCS cohort over time will enable researchers to monitor the effects of seasonality in addition to other time varying exposure variables upon respiratory symptoms symptoms. Exposures such as smoking, chronic co-morbidities and nursing attendance may be measured over a 5-year time frame for not only within the population but also in specific individuals. Confounding factors such as gender may be controlled for using stratification, matching, and statistical adjustment but these techniques account only for potential confounders that have been measured, not for unknown confounders.

Several problems were encountered during the developing the study, due to the complexity of establishing a birth cohort study. Many have been due to the complication of becoming accustomed to the complexity of the software required for the study. As with almost all research, delays have interrupted

the development of the LRBCS. These include; awaiting authorisation and communication between various organisations and administrative requirements. Additional delays occurred while waiting for funding applications to be processed before online software and recruitment could be purchased. In addition, a significant delay of several weeks occurred while waiting for the recruitment postcard order to be processed, proofed, revised and delivered. The time taken for each process during the development of the LRBCS has been summarised in figure 7.1.

An important ethical issue to consider was the recognition of deceased babies using Alder Hey Children's Hospital access to the NHS Personal Demographics Service so as to avoid making contact with a bereaved mother at any point during the study. This process was piloted during the recruitment to ensure maximum efficacy. Some issues were identified that included difficulty recognising babies, duplicated names with different identification number, individual babies with more than one identification number, infants registered with mothers surnames while recruitment postcards have collected different data. The need to improve the number of infants crossed referenced and differentiate between twins and triplets was also identified. These matters were resolved after meeting information analysts at Alder Hey hospital. It must be noted that this is not a flawless system however it is the most appropriate practical solution known and exceeds current best practice in use by routine NHS services.

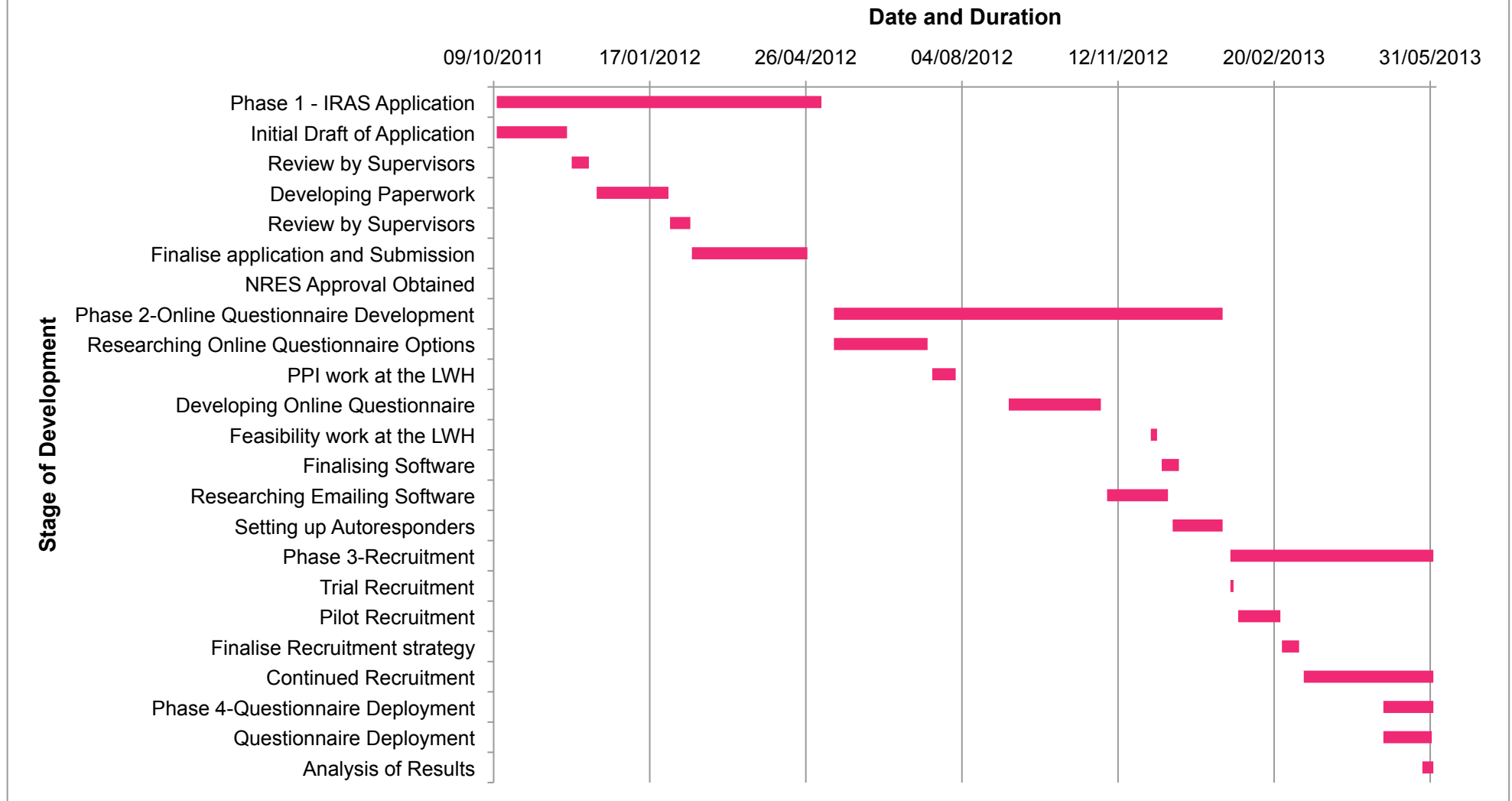
During questionnaire deployment some issues were identified. These included, the need to validate addresses of participants receiving postal questionnaires and the importance of responding to participants comments. Results from respondent to the initial questionnaire during the pilot period of the study, prompted researchers to include additional questions to the initial questionnaire. These included questions exploring interaction with healthcare services such as the GP and hospital visits, in addition to children sharing a room and nursery attendance. Adobe FormsCentral permits the addition of questions during deployment of an existing questionnaire. A method of setting up automated reminder emails was

difficult to identify, particularly within the financial constraints of the study budget. The discovery of a viable option for questionnaire deployment via an automated email service was imperative to the study's success. MailChimp® has proved to be a viable option, particularly with the ability to monitor opening rates, and set up automated reminders if the questionnaire URL has not been clicked. Not only do these features aid the research team when sending reminders but additionally enable the prompt identification of any problems with the questionnaire deployment.

It must be noted that this study is at a nascent stage and so conclusions may only be drawn once data has been received and formally analysed. As no significant body of results has yet been obtained, the implications of this research at present are very limited. Once the study is complete or a substantial amount of data has been collected and analysed, the implications of the LRBCS may be determined. The next step for this study is formal analysis of the results obtained from the questionnaires. This could not take place had the preliminary work for this study not been undertaken.



**Figure 7.1: Gantt Chart showing the development of the LRBCS over the course of the MPhil**



## 7.2 Strengths of the Study

The LRBCS benefits from several strengths. The use of a standardised outcome measure, developed by experienced paediatricians, has been pre-validated in the cohort of interest. This is a valuable tool not only for assessing respiratory symptoms but also for assessing the impact of children's respiratory symptoms upon the child and also their parents. Demographic and exposure questions cover a large range of details that explore the risk factors for respiratory conditions in preschool children.

The study aims to recruit a large, representative sample. Single site recruitment at the LWH provides an optimum base for recruitment, making recruitment easier to implement, manage and maintain. The LWH is also the predominant site for maternity services for mothers living within Liverpool postcodes. A personal approach maximises numbers recruited and is also a method recommended by previous studies. Recruitment to date has been very successful, as discussed in chapter six of this thesis.

As a whole population birth cohort, the LRBCS portrays a more accurate representation of the Liverpool population, from a well-defined study area within L1-L38. Liverpool is an ideal area for exploring deprivation and its effect upon the respiratory health of preschool children, as the city suffers from high levels of deprivation<sup>148</sup>. Collection of infant's entire postcodes means that more accurate IMD scores for individual postcodes may be used to measure deprivation and be matched with respiratory symptoms and conditions. The results of this study should be applicable to the whole of the Liverpool population.

The nature of the longitudinal study design offers several strengths. Cohort studies are perceived as the best observational study design as they are able to look at multiple outcomes<sup>82, 83</sup>. Information for the LRBCS will be collected at repeated time points over a long follow up period of 5 years. The LRBCS will link data longitudinally, using unique identification numbers given to each infant recruited into the cohort. Longitudinal studies are needed to study developmental sequences and are able to provide information about individual change; this is particularly useful when mapping respiratory symptoms. They also provide the opportunity to investigate the stability and continuity of symptoms over time and participants are able to serve as their own controls. A key strength of a longitudinal study is the ability to measure change in outcomes and/or exposures at the individual level. In addition, they provide an opportunity to measure incidence and relative risk of a disease directly within the cohort.

Involving patients in every possible aspect of the design and development of the LRBCS, enabled researchers to tailor the study method, questionnaire and recruitment material, to appeal to target population. This is a particularly important and valuable feature of the LRBCS. Furthermore, using mostly online questionnaires reduces the environmental impact of the research, consistent with carbon reduction guidelines by the Medical Research Council<sup>270</sup>.

### 7.3 Study Limitations

Despite the strengths of the LRBCS, there are limitations that must also be considered. The exclusion criterion includes non-English speaking participants, not only due to difficulty with recruitment, but also the complexity with regards to providing translated versions of the questionnaire. A translated questionnaire must be re-validated in that particular language. Not only are numerous translations not feasible, neither is the validation of the questionnaire for each different language, given the resources for this study. This exclusion criterion may affect the demographics and data collected, and must be taken into account when analysing data as the study cohort may not have the ethnic diversity of today's population. Excluding children taken into care is a regrettable necessity. The success of this study relies upon researchers maintaining contact with the parents or guardians of the children recruited, as the children themselves are too young and unable to complete the questionnaire. It would be near impossible to maintain contact with the guardians of children taken into care. This may distort the study's representation of the population.

A small research team results in limited availability of time and resources. The administrative burden of this particular study is sizeable, as with other cohort studies. Although the email scheduling software sends automated emails, reducing the requirement for questionnaires to be sent individually, the system needs to be carefully monitored on a regular basis. Postal questionnaires must be prepared, organised and deployed, while postal respondents must be manually inputted into the database. Administrative requirements are discussed in more detail in chapter six.

Inexperienced research staff is both an advantage and limitation in itself. An MPhil student in charge of the study reduces the financial burden, and provides a valuable experience for junior researchers but may incur problems. However supervision by senior and experienced staff may alleviate the majority of these problems. The inexperience of the student may introduce error into the study. The accuracy of data input is imperative particularly for longitudinal analysis. Errors in contact details compromises online questionnaire deployment and lack of organisation may prevent questionnaires from being deployed, whilst data errors may cause difficulty when linking data longitudinally. The study's success is therefore, reliant upon the work put in by the MPhil students themselves.

As this is a local population study of one specified city, results may not be representative of the general UK population. However results, particularly with regards to deprivation may be translatable to other areas of the UK with similar demographics. Loss to follow up weakens the quality of the data collected by a cohort study but is inevitable in a large cohort. The research team have enforced strategies to attempt to minimise attrition. These methods consist of frequent email reminders, in the form of three emails and one text message or phone call. An automated 'birthday email' will be sent to the mothers of all babies on the day of each birthday up until the age of five. This provides an opportunity for the study team to maintain contact with mothers on a more frequent basis, in a friendly and non-invasive manner. When completing each individual questionnaire, participants are also invited to join a mailing list to receive an optional, quarterly newsletter that includes details about the study's progress, detailing recruitment.

## 7.4 Potential Bias and Confounding Factors in Birth Cohort Studies

Attrition is one of the most important sources of bias, particularly as it is possible to lose sections of the population e.g. less affluent groups. This can have significant consequences on the quality of data and will have an impact on the efficacy of the study to reflect the true history of preschool respiratory symptoms in Liverpool. Particularly if subjects that are followed for the full study period, differ from subjects who discontinue follow-up. Analysts must consider this when analysing data otherwise summaries will not be representative of the original target population.

Selection bias is an additional factor to consider during recruitment, particularly for a study that will be conducted primarily using an online outcome measure. Researchers may correct for this by weighting specific population groups, particularly those that are underrepresented. Previous studies have raised a number of issues with regards to research using online surveys in research as participants are regarded as better educated and younger, so may not provide a representative sample of the population<sup>191, 271</sup>. Recruitment from a tertiary hospital such as the LWH, may also induce a proportion of selection bias as they may include a larger proportion of babies with co-morbidities and complicated births. The LWH has a specialist care baby unit, so may include a higher than average proportion of premature babies. To account for this the research team have chosen to limit recruitment to the Liverpool postcode. Some potential recruits may be lost due to the maternity services offered at Whiston Hospital and Ormskirk Hospital. This may occur from the surrounding postcodes such as L34-36 around Whiston Hospital and L31-L33 around Ormskirk Hospital.

In addition, the recruitment method does not accommodate for home births. Current data available for home birth is inconsistent, unreliable and out of date. Thus it is difficult to establish the number of babies missed from recruitment due to this factor, in particular the demographics of this cohort. HES and the Independent Midwives Association (IMA) database have excluded this data from publications due to the poor data coverage. Home

births should be reported nationally but this data is reliant upon completion by the midwife. The only available data available is provided by Birth UK, which reports that 1.2% of births in Liverpool (2006) were home births and according to the Office of National Statistics 2% births in the North West are home births. However specific and up to date data for regions within the North West is not available, subsequently it is impossible to estimate the demographic of mothers in Liverpool who deliver at home.

Although sample selection in cohort studies may alter the confounding patterns originally present in the general population, this does not necessarily introduce selection bias in the exposure–outcome estimates, as sample selection may reduce some of the residual confounding present in the general population<sup>272</sup>.

Migration bias is due to the movement of study participants outside the community or location of interest. A study by Katusic acknowledged the extreme effort to assemble and maintain a birth cohort study in an increasingly mobile society<sup>273</sup>. This however, may be combated by electronic contact via email, which allows the study team to regularly updating participant's contact details. The LRBCS does this by providing a link to a screen for participants to update their contact details, including addresses on receipt of email, birthday email sent and there is also an additional link on the study's website, inviting participants to update their contact details. During questionnaire completion, participants are asked if their contact details have changed and if they indicate that they have, they are then asked to provide their contact details before they can continue with the questionnaire. Migration bias has been considered and will be accounted for during data analysis by the LRBCS study team. Any mothers moving outside the Liverpool postcodes after expressing their interest in the study by completing a recruitment postcard will continue their involvement if they so wish. A comparison between the study cohort and children who emigrated from the cohort will be made to ensure that the study population representative of the entire birth cohort.

Recall bias should also be considered, particularly with an outcome measure that requires parents to retrospectively report their children's respiratory symptoms over the last three months. Exploring symptoms at multiple time-points assists in cutting down recall bias. The questionnaires authors Powell et al determined that short-term parental recall (three months and under) would be most reliable. Missing data also impedes on data quality. The online questionnaire minimises this, as the majority of the questions have to be completed before the respondent may complete the questionnaire while the postal questionnaire poses challenges in this area.

## 7.5 Future Work and Data Analysis

### 7.5.1 Future Work

Immediate, future work involves the continuation of recruitment, maintaining a maximum recruitment strategy. Personal recruitment must be continued in order to maintain reasonable recruitment figures. Moreover, the recruitment strategy should be reviewed regularly for flaws or potential areas for improvement. Statistics from recruitment so far emphasise the importance of this method. Particularly as the QR-sign up method has yielded only one participant, as has the post-boxes. Although these are valuable additional methods that require little maintenance, they must not be relied upon to continue recruitment.

Once questionnaires are returned, the data must be extracted and exported into SPSS for data analysis. A reasonable volume is required to maintain this study. However results from a previous study suggest significant results may be obtained from as little as 80 participants. However to date, the LRBCS has successfully recruited and received completed initial questionnaires from over 100 mothers over a period of 6 weeks following the four months since the study began. Current figures demonstrate that 22% of mothers who expressed an interest in the study, consented to take part in the LRBCS in addition to completing the initial



questionnaire. With over 1,500 infants mothers having expressed an interest in the study to date, a minimum of 330 respondents to the initial questionnaire are likely.

Future considerations include developing a mobile application for completing the questionnaire. This will add to the usability of the online questionnaire and may also include built in reminders for completing the questionnaire. The newsletter content should also be carefully considered and regularly deployed. A total of 62% of respondents to the initial questionnaire to date have signed up to the LRBCS newsletter, indicating that the majority of respondents would like to receive updates from the research team. It may be useful to include details regarding respiratory conditions, and how to recognise these conditions in the newsletter. Preliminary results may also encourage parents to respond.

Data and results obtained may provide a basis for applications to be made for further funding. Large birth cohort studies require substantial maintenance costs. Although conducting the majority of this study online reduces some financial requirements, funding is required for online survey software subscriptions, in addition to email, texts, and study material such as recruitment postcards. Further funding may enable the employment of a research assistant to potentially recruit full time and continue recruitment, provide opportunity to employ a statistical analyst, and possibly provide monetary or nonmonetary incentives to help reduce attrition.

During recruitment and questionnaire deployment, telephone reminders were not only identified as being time consuming for the study team but may be considered intrusive to study participants. The Short message service (SMS) is an alternative method to send non-intrusive reminders to participants that may be read at their earliest convenience. MailChimp® offers an opportunity link to SMS message reminder lists to an online text service that allows SMS message to be sent to a list of subscribers from a sender named 'BabyStudy'. The LRBCS team has recently employed this method and although successful to date, it requires further development. To

date the research team received nine responses for the 100 SMS messages sent, whilst six additional participants have completed the questionnaire after receiving the SMS reminder.

Social media is an ever-growing field and its with regards to medical research has recently been explored<sup>274</sup>. The research team have considered creating a Facebook, Inc (Menlo Park, California, USA) and/or Twitter, Inc (San Francisco, California, USA) account in order to help promote the study, provide regular updates to mothers and provide an opportunity for feedback. However after researching current Facebook pages of other birth cohort studies it became apparent that the most successful pages were those that were well maintained and included a significant amount of interaction with the cohort. In contrast, the research team felt that Facebook pages that were poorly maintained compromised the professional image of the study. A professional Facebook and Twitter account is time consuming to maintain so researchers felt at present, accounts would not be necessary for the success of the study. However, they may be considered as a method in the future to minimise attrition. An optional seasonal study newsletter satisfies the requirements for updating participants while all questionnaires prompt feedback. The National Institute for Health Research Identity Guidelines offer guidance with regards to Social media and digital engagement<sup>275</sup>.

Another factor to consider is the possibility of linking to Hospital episode summary (HES) data and data from GP practices in order to access more data such as relevant diagnoses of acute and chronic conditions, medication and treatment. In order to do this additional ethical approval must be sought. Attrition is an important factor to minimise. Non-monetary factors for improving response rates may be considered such as tea bags included with postal questionnaires and vouchers included for respondents to the online questionnaires. The study team would also benefit from a doctor of philosophy student who would be a consistent member of the recruitment team that could manage the study and maintain and regulate administration while aiding with data analysis.

### 7.5.2 Data Analysis

Results from the questionnaires on Adobe® Forms Central will be uploaded to SPSS and analysed using the SPSS Statistical software. A member of the research team will input the data from paper questionnaires into Adobe FormsCentral manually. Rolling cumulative data analysis will be performed for the duration of the study. Univariate and multivariate analyses will be conducted to assess single and then multiple variables e.g. to compare domain scores of the LRSQ scores with exposures such as maternal smoking etc. Linear regression analysis will enable researchers to control for confounding factors such as age and gender.

If the recruited cohort is large enough and the shows a normal distribution then Chi-squared test will be used to determine whether there is any association between two categorical variables from the data collected. Structural equation analysis and multinomial regression analysis will also be used to assess any relationship between exposure/demographic variables and respiratory symptoms in addition to identifying casual factors.

Demographic data is particularly important to analyse, particularly with regards to social deprivation. This may be done as accurately as possible according to full postcodes acquired, using a new method developed by the University of Manchester called Geoconvert(<http://geoconvert.mimas.ac.uk>). This is also important as literature suggests potential bias when using online data collection methods.

Longitudinal data analysis is not without its challenges. Although they provide an opportunity to associate changes between exposures and outcomes of interest, observations are by definition, not independent and the direction causality can be complicated by any interference between the outcome and the exposure. Therefore researchers must account for dependency when analysing data. Analysis of a large variety of data also presents difficulties, using software, unbalanced designs, missing data and attrition.

Attrition in particular is known to occur more frequently within specific groups of people, particularly subjects with lower income, lower ages, and this is likely to create an offset in statistical results. The analysis of incomplete data also incurs problems. However attrition is known to occur more with some groups of people than with others. In particular, subjects with lower income, lower ages, and lower trip frequencies have a greater tendency to drop out, and this is likely to create an offset in statistical results.

The questionnaire validity and readability are additional factors to explore and assess. Readability may also be examined in more detail using an additional to the Flesch score previously conducted by Powell et al<sup>79</sup>. The Flesch Reading Ease Score (1948)<sup>276</sup> is designed for narrative-type materials, as is the Gunning's Fog index (FOG; Gunning, 1952)<sup>277</sup>. Contrastingly, a measure used to assess readability for non-narrative-type materials includes the FORECAST formula (Caylor & Sticht, 1973)<sup>278</sup>.

The LRBCS provides an opportunity to assess the LRSQ to using a much larger cohort than was used previously. Questionnaire verification can be assessed by two concepts; validity and reproducibility. Validity encompasses sensitivity and specificity, while reproducibility is a calculation of consistency, which identifies if there are major biases in questions. Two categories of validity may be assessed; these include internal and external validity<sup>279</sup>. Internal consistency may be assessed using Cronbach's Alpha coefficient while external validity may be assessed by inter-rater reliability.

When items or questions are used to form a scale, such as the Likert scale in the LRSQ, they need to show internal consistency. The Cronbach's Alpha coefficient aims to express extent to which individual items, such as domains within a questionnaire, measures the same concept. Now common practice in medical research, this coefficient is frequently used when multiple item measures of a construct or concept are employed particularly one-test measure that is easier to use in comparison to other estimates e.g. test-retest reliability estimates. Results of Cronbach's Alpha are expressed

as a number between zero and one. Each individual domain within the LRSQ will should be calculated rather than the entire questionnaire<sup>280</sup>. Thus Cronbach's alpha scores were calculated for the 8 domains of the LRSQ. Acceptable values range between 0.7 - 0.95<sup>280</sup>. Factors such as a small number of questions, poor interrelatedness or diverse questions may lower this result<sup>281</sup>. It has been noted that if the 'standardise item alpha' calculation in SPSS is higher than 'Cronbach's Alpha' then further evaluation using an equivalent measure of Internet consistency might be necessary<sup>281</sup>.

An additional feature of a questionnaire that requires further assessment is it's ability to detect change and a longitudinal data sample provides an ideal platform to assess this<sup>282</sup>. Powell et al suggest also suggested that a more detailed analysis of criterion validity along with responsiveness of questionnaire is required using a larger population and including children with different phenotypes of wheezy illness<sup>79</sup>.

## 7.6 Conclusion

The Liverpool Respiratory Birth Cohort Study has been successfully designed, developed and initiated, having progressed through the protocol development, ethical approval, outcome measure design and finalising the recruitment strategy. This study may proceed to run for a minimum of a further 6 years and will produce a large variety of valuable data detailing the respiratory health and characteristics of the preschool Liverpool population. Future analysis will enable the exploration of demographic and exposure factors affecting the respiratory health of the Liverpool preschool population.

## 8 References

1. NETSCC. NETSCC Glossary: Feasibility and Pilot studies. 2013;2013.
2. Semple MG, Taylor-Robinson D, C, Department of Public H, Policy UoLLUK, Steven L, Department of Biostatistics UoLLUK, et al. Household Tobacco Smoke and Admission Weight Predict Severe Bronchiolitis in Infants Independent of Deprivation: Prospective Cohort Study. *PLOS ONE* 2011;6.
3. Frank PI, Morris JA, Hazell ML, Linehan MF, Frank TL. Long term prognosis in preschool children with wheeze: longitudinal postal questionnaire study 1993-2004. In: *BMJ*. England, 2008:1423-6.
4. Koopman LP, Brunekreef B, De Jongste JC, Neijens HJ. Definition of respiratory symptoms and disease in early childhood in large prospective birth cohort studies that predict the development of asthma. *Pediatric Allergy and Immunology* 2001;12(3):118-24.
5. Linehan MF, Hazell ML, Frank TL, Frank PI. Prevalence of respiratory symptoms in under 5s: 1993 to 2001. *Arch Dis Child* 2005;90(5):516-9.
6. Lowe LA, Simpson A, Woodcock A, Morris J, Murray CS, Custovic A. Wheeze phenotypes and lung function in preschool children. *Am J Respir Crit Care Med* 2005;171(3):231-7.
7. Morgan WJ, Stern DA, Sherrill DL, Guerra S, Holberg CJ, Guilbert TW, et al. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. *Am J Respir Crit Care Med* 2005;172(10):1253-8.
8. Semple MG, Smyth RL. *Pathophysiology. Lessons from human respiratory syncytial virus bronchiolitis and acute wheezing episodes in infants*, 2006. (Asthma ).
9. Smith JA, Drake R, Simpson A, Woodcock A, Pickles A, Custovic A. Dimensions of respiratory symptoms in preschool children: population-based birth cohort study. *Am J Respir Crit Care Med* 2008;177(12):1358-63.
10. Morgan WJ, Stern DA, Sherrill DL, Guerra S, Holberg CJ, Guilbert TW, et al. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. *Am J Respir Crit Care Med* 2005;172(10):1253-8.
11. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995;332(3):133-8.
12. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995;332(3):133-8.
13. Brooke AM, Lambert PC, Burton PR, Clarke C, Luyt DK, Simpson H. The natural history of respiratory symptoms in preschool children. *American Journal of Respiratory and Critical Care Medicine* 1995;152(6):1872-8.
14. Linehan MF, Hazell ML, Frank TL, Frank PI. Prevalence of respiratory symptoms in under 5s: 1993 to 2001. *Archives of Disease in Childhood* 2005;90(5):516-9.

15. Gold DR, Burge HA, Carey V, Milton DK, Platts-Mills T, Weiss ST. Predictors of repeated wheeze in the first year of life: the relative roles of cockroach, birth weight, acute lower respiratory illness, and maternal smoking.
16. Lowe L, Murray CS, Custovic A, Simpson BM, Kissen PM, Woodcock A. Specific airway resistance in 3-year-old children: a prospective cohort study. *The Lancet* 2002;359(9321):1904-8.
17. P.J.F.M.Merkus UFa. *Paediatric Lung Function*. European Respiratory Society Journals Ltd, 442 Glossop Road, Sheffield, S10 2PX, UK: European Respiratory Society Journals Ltd, 2010.
18. Nystad W, Samuelsen SO, Nafstad P, Edvardsen E, Stensrud T, Jaakkola JJ. Feasibility of measuring lung function in preschool children. *Thorax* 2002;57(12):1021-7.
19. Samet JM. A Historical and Epidemiologic Perspective on Respiratory Symptom Questionnaires. *American Journal of Epidemiology* 1978;108(6):435-46.
20. Luyt DK, Burton PR, Simpson H. Epidemiological study of wheeze, doctor diagnosed asthma, and cough in preschool children in Leicestershire. *BMJ* 1993;306(6889):1386-90.
21. Strippoli M-PF, Silverman M, Michel G, Kuehni CE. A parent-completed respiratory questionnaire for 1-year-old children: repeatability. *Archives of Disease in Childhood* 2007;92(10):861-5.
22. Clifford RD, Radford M, Howell JB, Holgate ST. Prevalence of respiratory symptoms among 7 and 11 year old schoolchildren and association with asthma. *Archives of Disease in Childhood* 1989;64(8):1118-25.
23. Samet JM. Epidemiologic approaches for the identification of asthma\*. *CHEST Journal* 1987;91(6\_Supplement):74S-8S.
24. Timonen KL, Nielsen J, Schwartz J, Gotti A, Vondra V, Gratziau C, et al. Chronic respiratory symptoms, skin test results, and lung function as predictors of peak flow variability. *Am J Respir Crit Care Med* 1997;156(3 Pt 1):776-82.
25. Hyland ME. Quality-of-life assessment in respiratory disease: an examination of the content and validity of four questionnaires. *Pharmacoeconomics* 1992;2(1):43-53.
26. Bai J, Peat JK, Berry G, Marks GB, Woolcock AJ. Questionnaire items that predict asthma and other respiratory conditions in adults. *Chest* 1998;114(5):1343-8.
27. Barley EA, Jones PW. A comparison of global questions versus health status questionnaires as measures of the severity and impact of asthma. *Eur Respir J* 1999;14(3):591-6.
28. Nihlen U, Montnemery P, Lindholm LH, Lofdahl CG. Detection of chronic obstructive pulmonary disease (COPD) in primary health care: role of spirometry and respiratory symptoms. *Scand J Prim Health Care* 1999;17(4):232-7.
29. Hermiz O, Comino E, Marks G, Daffurn K, Wilson S, Harris M. Randomised controlled trial of home based care of patients with chronic obstructive pulmonary disease. *BMJ* 2002;325(7370):938.
30. Narang I, Rosenthal M, Cremonesini D, Silverman M, Bush A. Longitudinal evaluation of airway function 21 years after preterm birth. In: *Am J Respir Crit Care Med*. United States, 2008:74-80.

31. Jones PW. St George's Respiratory Questionnaire Manual. June 2009.
32. Hyland ME. The Living with Asthma Questionnaire. *Respiratory Medicine* 1991;85, Supplement 2(0):13-6.
33. Graham NM. The epidemiology of acute respiratory infections in children and adults: a global perspective. *Epidemiologic reviews* 1990;12:149-78.
34. Panzer PC, van Cauvenberg P, Bousquet J. [Global Allergy and Asthma European Network (GA2LEN) addresses the epidemic of allergy and asthma]. *Cas Lek Cesk* 2010;149(1):32-7.
35. Cotes JE, Chinn DJ. MRC questionnaire (MRCQ) on respiratory symptoms. *Occupational Medicine* 2007;57(5):388.
36. Barr JT, Schumacher GE, Freeman S, LeMoine M, Bakst AW, Jones PW. American translation, modification, and validation of the St. George's Respiratory Questionnaire. In: *Clin Ther*. United States, 2000:1121-45.
37. Torén K, Blanc PD. Asthma caused by occupational exposures is common – A systematic analysis of estimates of the population-attributable fraction. *BMC Pulmonary Medicine* 2009;9:7.
38. Wilson CB, Jones PW, O'Leary CJ, Cole PJ, Wilson R. Validation of the St. George's Respiratory Questionnaire in bronchiectasis. *Am J Respir Crit Care Med* 1997;156(2 Pt 1):536-41.
39. Camelier A, Rosa FW, Salim C, Nascimento OA, Cardoso F, Jardim JR. Using the Saint George's Respiratory Questionnaire to evaluate quality of life in patients with chronic obstructive pulmonary disease: validating a new version for use in Brazil. In: *J Bras Pneumol*. Brazil, 2006:114-22.
40. Ferrer M, Villasante C, Alonso J, Sobradillo V, Gabriel R, Vilagut G, et al. Interpretation of quality of life scores from the St George's Respiratory Questionnaire. *European Respiratory Journal* 2002;19(3):405-13.
41. Yang SY, Kang W, Yeo Y, Park YC, Bae YJ, Kim YS, et al. Reliability and validity of Wisconsin Upper Respiratory Symptom Survey, Korean version. In: *J Epidemiol*. Japan, 2011:313-8.
42. B. Barrett REB, M. P. Mundt, G. R. Thomas, S. K. Barlow, A. D. Highstrom, and M. Bahrainian. Validation of a short form Wisconsin Upper Respiratory Symptom Survey (WURSS-21). *Health and Quality of Life Outcomes*;7.
43. Ronmark EP, Ekerljung L, Lotvall J, Toren K, Ronmark E, Lundback B. Large scale questionnaire survey on respiratory health in Sweden: effects of late- and non-response. In: *Respir Med*. England, 2009:1807-15.
44. Kanter LJ, Siegel CJ, Snyder CF, Pelletier EM, Buchner DA, Goss TF, et al. Impact of respiratory symptoms on health-related quality of life and medical resource utilization of patients treated by allergy specialists and primary care providers. In: *Ann Allergy Asthma Immunol*. United States, 2002:139-47.
45. Jackson G DHSIBA. Transmission of the common cold to volunteers under controlled conditions: I. the common cold as a clinical entity. *A.M.A. Archives of Internal Medicine* 1958;101(2):267-78.



46. Juniper EF, Buist AS, Cox FM, Ferrie PJ, King DR. Validation of a standardized version of the asthma quality of life questionnaire\*. *CHEST Journal* 1999;115(5):1265-70.
47. Bayliss MS, Espindle DM, Buchner D, Blaiss MS, Ware JE. A new tool for monitoring asthma outcomes: the ITG Asthma Short Form. *Qual Life Res* 2000;9(4):451-66.
48. Juniper EF, Gruffydd-Jones K, Ward S, Svensson K. Asthma Control Questionnaire in children: validation, measurement properties, interpretation. *Eur Respir J* 2010;36(6):1410-6.
49. Soutar CA, Hurley JF, Miller BG, Cowie HA, Buchanan D. Dust concentrations and respiratory risks in coalminers: key risk estimates from the British Pneumoconiosis Field Research. *Occupational and Environmental Medicine* 2004;61(6):477-81.
50. Bakke P, Gulsvik A, Lilleng P, Overå O, Hanao R, Eide GE. Postal survey on airborne occupational exposure and respiratory disorders in Norway: causes and consequences of non-response. *Journal of Epidemiology and Community Health* 1990;44(4):316-20.
51. Kilpeläinen M, Terho EO, Helenius H, Koskenvuo M. Validation of a new questionnaire on asthma, allergic rhinitis, and conjunctivitis in young adults. *Allergy* 2001;56(5):377-84.
52. Susitaival P. *Tuohilampi Questionnaire for Epidemiological Studies of Contact Dermatitis and Atopy*: Finnish Institute of Occupational Health, 1996. <http://books.google.co.uk/books?id=YdUWAAAACAAJ>.
53. Wickman M, Kull I, Pershagen G, Nordvall SL. The BAMSE project: presentation of a prospective longitudinal birth cohort study. *Pediatr Allergy Immunol* 2002;13 Suppl 15:11-3.
54. Calverley PM, Nordyke RJ, Halbert RJ, Isonaka S, Nonikov D. Development of a population-based screening questionnaire for COPD. *COPD* 2005;2(2):225-32.
55. Soutar CA, Hurley JF, Miller BG, Cowie HA, Buchanan D. Dust concentrations and respiratory risks in coalminers: key risk estimates from the British Pneumoconiosis Field Research. *Occupational and Environmental Medicine* 2004;61(6):477-81.
56. Henry B, Aussage P, Grosskopf C, Goehrs JM. Development of the Cystic Fibrosis Questionnaire (CFQ) for assessing quality of life in pediatric and adult patients. *Qual Life Res* 2003;12(1):63-76.
57. Becklake MR. International union against tuberculosis and lung disease (IUATLD): initiatives in non-tuberculous lung disease. *Tuber Lung Dis* 1995;76(6):493-504.
58. Björnsson E, Plaschke P, Norrman E, Janson C, Lundback B, Rosenhall A, et al. Symptoms related to asthma and chronic bronchitis in three areas of Sweden. *Eur Respir J* 1994;7(12):2146-53.
59. Lundback B, Nystrom L, Rosenhall L, Stjernberg N. Obstructive lung disease in northern Sweden: respiratory symptoms assessed in a postal survey. *European Respiratory Journal* 1991;4(3):257-66.
60. Andersson K, Fagerlund I, Bodin L, Ydreborg B. Questionnaire as an Instrument When Evaluating Indoor Climate. In: *Healthy Buildings*, 1988.
61. Frisk M, Magnuson A, Kiviloog J, Ivarsson AB, Kamwendo K. Increased occurrence of respiratory symptoms is associated with

- indoor climate risk indicators - a cross-sectional study in a Swedish population. *Respir Med* 2007;101(9):2031-5.
62. Taussig LM, Wright AL, Morgan WJ, Harrison HR, Ray CG. The Tucson Children's Respiratory Study. I. Design and implementation of a prospective study of acute and chronic respiratory illness in children. *Am J Epidemiol* 1989;129(6):1219-31.
  63. Pride NB. Revision of the European Community for Coal and Steel Questionnaire on Respiratory Symptoms. *Eur Respir J* 1989;2(8):697-9.
  64. Paoletti P, Tonnesen P, Rodriguez-Roisin R. CEASE (Collaborative European Anti-Smoking Evaluation). A challenging multicenter trial organized by the European Respiratory Society. *Chest* 1993;103(5):1317-9.
  65. Birring SS, Prudon B, Carr AJ, Singh SJ, Morgan MDL, Pavord ID. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). *Thorax* 2003;58(4):339-43.
  66. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *European Respiratory Journal* 1995;8(3):483-91.
  67. Murphy KR, Zeiger RS, Kosinski M, Chipps B, Mellon M, Schatz M, et al. Test for Respiratory and Asthma Control in Kids (TRACK): A caregiver-completed questionnaire for preschool-aged children. *The Journal of allergy and clinical immunology* 2009;123(4):833-9.e9.
  68. Austin JB, Kaur B, Anderson HR, Burr M, Harkins LS, Strachan DP, et al. Hay fever, eczema, and wheeze: a nationwide UK study (ISAAC, international study of asthma and allergies in childhood). *Archives of Disease in Childhood* 1999;81(3):225-30.
  69. Williams JEA, Singh SJ, Sewell L, Guyatt GH, Morgan MDL. Development of a self-reported Chronic Respiratory Questionnaire (CRQ-SR). *Thorax* 2001;56(12):954-9.
  70. Morris P. Epidemiology Standardisation Project II. Recommended respiratory disease questionnaires for use with adults and children in epidemiological research. *Am Rev Respir Dis* (1978);118 (suppl):7-53.
  71. Juniper EF, Guyatt GH, Feeny DH, Ferrie PJ, Griffith LE, Townsend M. Measuring quality of life in the parents of children with asthma. *Qual Life Res* 1996;5(1):27-34.
  72. Usherwood TP, Scrimgeour A, Barber JH. Questionnaire to measure perceived symptoms and disability in asthma. *Archives of Disease in Childhood* 1990;65(7):779-81.
  73. Quittner AL, Buu A, Messer MA, Modi AC, Watrous M. Development and validation of The Cystic Fibrosis Questionnaire in the United States: a health-related quality-of-life measure for cystic fibrosis. *Chest* 2005;128(4):2347-54.
  74. Strippoli MP, Silverman M, Michel G, Kuehni CE. A parent-completed respiratory questionnaire for 1-year-old children: repeatability. *Arch Dis Child* 2007;92(10):861-5.

75. Luyt DK, Burton P, Brooke AM, Simpson H. Wheeze in preschool children and its relation with doctor diagnosed asthma. *Arch Dis Child* 1994;71(1):24-30.
76. Frank T, Frank P, McNamee R, Wright T, Hannaford P, Morrison J, et al. Assessment of a simple scoring system applied to a screening questionnaire of asthma in children aged 5-15 yrs. *European Respiratory Journal* 1999;14(5):1190-7.
77. Custovic A, Simpson BM, Murray CS, Lowe L, Woodcock A, on behalf of the NACMA, et al. The National Asthma Campaign Manchester Asthma and Allergy Study. *Pediatric Allergy and Immunology* 2002;13:32-7.
78. Simpson BM, Custovic A, Simpson A, Hallam CL, Walsh D, Marolia H, et al. NAC Manchester Asthma and Allergy Study (NACMAAS): risk factors for asthma and allergic disorders in adults. *Clinical & Experimental Allergy* 2001;31(3):391-9.
79. Powell CVE, McNamara P, Solis A, Shaw NJ. A parent completed questionnaire to describe the patterns of wheezing and other respiratory symptoms in infants and preschool children. *Archives of Disease in Childhood* 2002;87(5):376-9.
80. Trinick R, Southern KW, McNamara PS. Assessing the Liverpool Respiratory Symptom Questionnaire in children with cystic fibrosis. *European Respiratory Journal* 2012;39(4):899-905.
81. Pickles R SMG. Assessing preschool respiratory symptoms post RSV bronchiolitis using the Liverpool Respiratory Symptom Questionnaire. Institute of Translational Medicine, University of Liverpool; 2012.
82. Grimes DA, Schulz KF. Cohort studies: marching towards outcomes. *Lancet* 2002;359(9303):341-5.
83. Watts G. In for the long haul. *BMJ* 2011;342.
84. Wadsworth M, Kuh D, Richards M, Hardy R. Cohort Profile: The 1946 National Birth Cohort (MRC National Survey of Health and Development). *International Journal of Epidemiology* 2006;35(1):49-54.
85. Alfred T, Ben-Shlomo Y, Cooper R, Hardy R, Cooper C, Deary IJ, et al. Genetic markers of bone and joint health and physical capability in older adults: the HALCyon programme. *Bone* 2013;52(1):278-85.
86. Davis DH, Muniz Terrera G, Keage H, Rahkonen T, Oinas M, Matthews FE, et al. Delirium is a strong risk factor for dementia in the oldest-old: a population-based cohort study. *Brain* 2012;135(Pt 9):2809-16.
87. Gardner MP, Lightman S, Sayer AA, Cooper C, Cooper R, Deeg D, et al. Dysregulation of the hypothalamic pituitary adrenal (HPA) axis and physical performance at older ages: an individual participant meta-analysis. *Psychoneuroendocrinology* 2013;38(1):40-9.
88. Kuh D, Cooper R, Richards M, Gale C, von Zglinicki T, Guralnik J. A life course approach to healthy ageing: the HALCyon programme. *Public Health* 2012;126(3):193-5.
89. Mann SL, Wadsworth ME, Colley JR. Accumulation of factors influencing respiratory illness in members of a national birth cohort and their offspring. *J Epidemiol Community Health* 1992;46(3):286-92.

90. Power C, Elliott J. Cohort profile: 1958 British birth cohort (National Child Development Study). *International Journal of Epidemiology* 2006;35(1):34-41.
91. Butler NR, Goldstein H, Ross EM. Cigarette Smoking in Pregnancy: Its Influence on Birth Weight and Perinatal Mortality. *BMJ* 1972;2(5806):127-30.
92. Strachan DP, Butland BK, Anderson HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. *BMJ* 1996;312(7040):1195-9.
93. Power C. A review of child health in the 1958 birth cohort: National Child Development Study. *Paediatric and Perinatal Epidemiology* 1992;6(1):81-110.
94. Lake JK, Power C, Cole TJ. Child to adult body mass index in the 1958 British birth cohort: associations with parental obesity. *Archives of Disease in Childhood* 1997;77(5):376-80.
95. Elliott J, Shepherd P. Cohort Profile: 1970 British Birth Cohort (BCS70). *International Journal of Epidemiology* 2006;35(4):836-43.
96. Maughan B, Taylor C, Taylor A, Butler N, Bynner J. Pregnancy Smoking and Childhood Conduct Problems: A Causal Association? *Journal of Child Psychology and Psychiatry* 2001;42(8):1021-8.
97. Taylor B, Wadsworth J. Maternal smoking during pregnancy and lower respiratory tract illness in early life. *Archives of Disease in Childhood* 1987;62(8):786-91.
98. Rush D, Cassano P. Relationship of cigarette smoking and social class to birth weight and perinatal mortality among all births in Britain, 5-11 April 1970. *J Epidemiol Community Health* 1983;37(4):249-55.
99. Jedrychowski W, Flak E. Maternal smoking during pregnancy and postnatal exposure to environmental tobacco smoke as predisposition factors to acute respiratory infections. *Environ Health Perspect* 1997;105(3):302-6.
100. Lewis S, Richards D, Bynner J, Butler N, Britton J. Prospective study of risk factors for early and persistent wheezing in childhood. *Eur Respir J* 1995;8(3):349-56.
101. Cable N, Bartley M, McMunn A, Kelly Y. Gender differences in the effect of breastfeeding on adult psychological well-being. *The European Journal of Public Health* 2011.
102. Smith K, Joshi H. The Millennium Cohort Study. *Popul Trends* 2002(107):30-4.
103. Joshi SDaH. *Millenium Cohort Study First Survey*. London: Insitute of Education, University of London, 2004.
104. Hansen K, Joshi H. *Millennium Cohort Study Second Survey: A User's Guide to Initial Findings*: Centre for Longitudinal Studies, Institute of Education, University of London, 2007. <http://eprints.ioe.ac.uk/2734/>.
105. Quigley MA, Kelly YJ, Sacker A. Breastfeeding and Hospitalization for Diarrheal and Respiratory Infection in the United Kingdom Millennium Cohort Study. *Pediatrics* 2007;119(4):e837-e42.
106. Smith TC. Linking exposures and health outcomes to a large population-based longitudinal study: the Millennium Cohort Study. *Mil Med* 2011;176(7 Suppl):56-63.

107. Panico L, Bartley M, Marmot M, Nazroo JY, Sacker A, Kelly YJ. Ethnic variation in childhood asthma and wheezing illnesses: findings from the Millennium Cohort Study. *International Journal of Epidemiology* 2007;36(5):1093-102.
108. Kuehni CE, Brooke AM, Strippoli M-PF, Spycher BD, Davis A, Silverman M. Cohort Profile: The Leicester Respiratory Cohorts. *International Journal of Epidemiology* 2007;36(5):977-85.
109. Kuehni C, Brooke A, Silverman M. Prevalence of wheeze during childhood: retrospective and prospective assessment. *European Respiratory Journal* 2000;16(1):81-5.
110. Goodfellow SA, Rolfe EM, Golding J. Cohort Profile: The Isle of Man Birth Cohort Study. *International Journal of Epidemiology* 2012.
111. European Longitudinal Study of Pregnancy and Childhood (ELSPAC). *Paediatric and Perinatal Epidemiology* 1989;3(4):460-9.
112. Children ALSoPa. *Avon Longitudinal Study of Parents and Children*. 2012. <http://www.bristol.ac.uk/alspac/> (accessed).
113. Boyd A, Golding J, Macleod J, Lawlor DA, Fraser A, Henderson J, et al. Cohort Profile: The 'Children of the 90s'--the index offspring of the Avon Longitudinal Study of Parents and Children. *Int J Epidemiol* 2012.
114. Fraser A, Macdonald-Wallis C, Tilling K, Boyd A, Golding J, Davey Smith G, et al. Cohort Profile: The Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. *International Journal of Epidemiology* 2012.
115. Dewey C, Fleming P, Golding J. Does the supine sleeping position have any adverse effects on the child? II. Development in the first 18 months. ALSPAC Study Team. *Pediatrics* 1998;101(1):E5.
116. Lack G, Fox D, Northstone K, Golding J. Factors Associated with the Development of Peanut Allergy in Childhood. *New England Journal of Medicine* 2003;348(11):977-85.
117. Hibbeln JR, Davis JM, Steer C, Emmett P, Rogers I, Williams C, et al. Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study. *Lancet* 2007;369(9561):578-85.
118. Henderson J, Northstone K, Lee SP, Liao H, Zhao Y, Pembrey M, et al. The burden of disease associated with filaggrin mutations: a population-based, longitudinal birth cohort study. *J Allergy Clin Immunol* 2008;121(4):872-7 e9.
119. Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science* 2007;316(5826):889-94.
120. Timpson NJ, Emmett PM, Frayling TM, Rogers I, Hattersley AT, McCarthy MI, et al. The fat mass- and obesity-associated locus and dietary intake in children. *Am J Clin Nutr* 2008;88(4):971-8.
121. Shaheen SO, Newson RB, Sherriff A, Henderson AJ, Heron JE, Burney PG, et al. Paracetamol use in pregnancy and wheezing in early childhood. *Thorax* 2002;57(11):958-63.
122. Cookson H, Granell R, Joinson C, Ben-Shlomo Y, Henderson AJ. Mothers' anxiety during pregnancy is associated with asthma in their children. *J Allergy Clin Immunol* 2009;123(4):847-53 e11.

123. Sherriff A, Farrow A, Golding J, Henderson J. Frequent use of chemical household products is associated with persistent wheezing in pre-school age children. *Thorax* 2005;60(1):45-9.
124. Sherriff A, Golding J. Hygiene levels in a contemporary population cohort are associated with wheezing and atopic eczema in preschool infants. *Arch Dis Child* 2002;87(1):26-9.
125. Wright J, Small N, Raynor P, Tuffnell D, Bhopal R, Cameron N, et al. Cohort profile: The Born in Bradford multi-ethnic family cohort study. *International Journal of Epidemiology* 2012.
126. Lumb KM, Congdon PJ, Lealman GT. A comparative review of Asian and British-born maternity patients in Bradford, 1974-8. *Journal of Epidemiology and Community Health* 1981;35(2):106-9.
127. Vrijheid M, Casas M, Bergstrom A, Carmichael A, Cordier S, Eggesbo M, et al. European birth cohorts for environmental health research. *Environ Health Perspect* 2012;120(1):29-37.
128. Olsen J, Melbye M, Olsen SF, Sørensen TIA, Aaby P, Nybo Andersen A-M, et al. The Danish National Birth Cohort - its background, structure and aim. *Scandinavian Journal of Public Health* 2001;29(4):300-7.
129. Magnus P, Irgens LM, Haug K, Nystad W, Skjærven R, Stoltenberg C, et al. Cohort profile: The Norwegian Mother and Child Cohort Study (MoBa). *International Journal of Epidemiology* 2006;35(5):1146-50.
130. Jaddoe VW, van Duijn CM, van der Heijden AJ, Mackenbach JP, Moll HA, Steegers EA, et al. The Generation R Study: design and cohort update 2010. *European journal of epidemiology* 2010;25(11):823-41.
131. Taussig LM, Wright AL, Holberg CJ, Halonen M, Morgan WJ, Martinez FD. Tucson Children's Respiratory Study: 1980 to present. *J Allergy Clin Immunol* 2003;111(4):661-75; quiz 76.
132. Martinez FD. What have we learned from the Tucson Children's Respiratory Study? *Paediatr Respir Rev* 2002;3(3):193-7.
133. !!! INVALID CITATION !!!
134. Martinez FD, Wright AL, Holberg CJ, Morgan WJ, Taussig LM. Maternal Age as a Risk Factor for Wheezing Lower Respiratory Illnesses in the First Year of Life. *American Journal of Epidemiology* 1992;136(10):1258-68.
135. Nieuwenhuijsen M, Casas M, Vrijheid M. Environmental Health Risks in European Birth Cohorts. *Epidemiology* 2011;22(1):S276  
10.1097/01.ede.0000392547.95364.bb.
136. Hubbard R. The burden of lung disease. *Thorax* 2006;61(7):557-8.
137. England PH. Atlas of Variation for Respiratory Disease. 2013;2013.
138. Brabin B, Smith M, Milligan P, Benjamin C, Dunne E, Pearson M. Respiratory morbidity in Merseyside schoolchildren exposed to coal dust and air pollution. *Archives of Disease in Childhood* 1994;70(4):305-12.
139. Rizwan S, Reid J, Kelly Y, Bundred PE, Pearson M, Brabin BJ. Trends in childhood and parental asthma prevalence in Merseyside, 1991–1998. *Journal of Public Health* 2004;26(4):337-42.
140. Kelly YJ, Brabin BJ, Milligan P, Heaf DP, Reid J, Pearson MG. Maternal asthma, premature birth, and the risk of respiratory



- morbidity in schoolchildren in Merseyside. *Thorax* 1995;50(5):525-30.
141. Koshy G, Delpisheh A, Brabin BJ. Trends in prevalence of childhood and parental asthma in Merseyside, 1991-2006. In: *J Public Health (Oxf)*. England, 2010:488-95.
142. Trinder PM, Croft PR, Lewis M. Social class, smoking and the severity of respiratory symptoms in the general population. *J Epidemiol Community Health* 2000;54(5):340-3.
143. Cook DG, Strachan DP. Health effects of passive smoking. 3. Parental smoking and prevalence of respiratory symptoms and asthma in school age children. *Thorax* 1997;52(12):1081-94.
144. Payne RA, Abel GA. UK indices of multiple deprivation - a way to make comparisons across constituent countries easier. *Health Stat Q* 2012(53):22-37.
145. Morgan O, Baker A. Measuring deprivation in England and Wales using 2001 Carstairs scores. *Health Stat Q* 2006(31):28-33.
146. Council LC. *The Index of Multiple Deprivation 2010*. Liverpool City Council, Municipal Buildings, Dale Street, Liverpool L2 2DH: Liverpool City Council, 2011.
147. Government CaL. *The English Indices of Deprivation 2010*. March 2011. (978-1-4098-2924-9).
148. Council LC. *Annual Report of the Joint Director of Public Health*. Liverpool Primary Care Trust, 2011-2012.
149. Observatory CaMH. *Child Health Profile: Liverpool*. UK, 2013 March.
150. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. *American journal of respiratory and critical care medicine* 2012;163(5).
151. Hansen K. *Millennium Cohort Study: First, Second and Fourth Surveys: A Guide to the Datasets*. October 2012.  
[http://www.cls.ioe.ac.uk/page.aspx?&sitesectionid=866&sitesectionitle=The+age+7+survey+of+the+MCS+\(2008\)](http://www.cls.ioe.ac.uk/page.aspx?&sitesectionid=866&sitesectionitle=The+age+7+survey+of+the+MCS+(2008)) (accessed.
152. Semple MG, Taylor-Robinson DC, Lane S, Smyth RL. Household tobacco smoke and admission weight predict severe bronchiolitis in infants independent of deprivation: prospective cohort study. *PLoS one* 2011;6(7):e22425.
153. DiFranza JR, Aligne CA, Weitzman M. Prenatal and postnatal environmental tobacco smoke exposure and children's health. *Pediatrics* 2004;113(Supplement 3):1007-15.
154. Rona R, Gulliford M, Chinn S. Effects of prematurity and intrauterine growth on respiratory health and lung function in childhood. *BMJ: British Medical Journal* 1993;306(6881):817.
155. Todisco T, De Benedictis F, Iannacci L, Baglioni S, Eslami A, Todisco E, et al. Mild prematurity and respiratory functions. *European journal of pediatrics* 1993;152(1):55-8.
156. Dockery DW, Pope CA. Acute respiratory effects of particulate air pollution. *Annual review of public health* 1994;15(1):107-32.
157. Boezen HM, van der Zee SC, Postma DS, Vonk JM, Gerritsen J, Hoek G, et al. Effects of ambient air pollution on upper and lower respiratory symptoms and peak expiratory flow in children. *The Lancet* 1999;353(9156):874-8.

158. Chan K, Elliman A, Bryan E, Silverman M. Respiratory symptoms in children of low birth weight. *Archives of disease in childhood* 1989;64(9):1294-304.
159. Palta M, Sadek-Badawi M, Sheehy M, Albanese A, Weinstein M, McGuinness G, et al. Respiratory symptoms at age 8 years in a cohort of very low birth weight children. *American Journal of Epidemiology* 2001;154(6):521-9.
160. Spencer N, Logan S, Scholey S, Gentle S. Deprivation and bronchiolitis. *Archives of disease in childhood* 1996;74(1):50-2.
161. Deshpande S, Northern V. The clinical and health economic burden of respiratory syncytial virus disease among children under 2 years of age in a defined geographical area. *Archives of disease in childhood* 2003;88(12):1065-9.
162. Bråbäck L, Breborowicz A, Julge K, Knutsson A, Riiikjær MA, Vasar M, et al. Risk factors for respiratory symptoms and atopic sensitisation in the Baltic area. *Archives of disease in childhood* 1995;72(6):487-93.
163. Stein RT, Holberg CJ, Sherrill D, Wright AL, Morgan WJ, Taussig L, et al. Influence of Parental Smoking on Respiratory Symptoms during the First Decade of Life The Tucson Children's Respiratory Study. *American Journal of Epidemiology* 1999;149(11):1030-7.
164. Sly PD, Kusel MM, de Klerk NH, Holt PG, Keadze T, Johnston SL. Role of respiratory viruses in acute upper and lower respiratory tract illness in the first year of life: a birth cohort study. *The Pediatric infectious disease journal* 2006;25(8):680-6.
165. Osman L, Baxter-Jones A, Helms P. Parents' quality of life and respiratory symptoms in young children with mild wheeze. *European Respiratory Journal* 2001;17(2):254-8.
166. Bloemers BL, van Furth AM, Weijerman ME, Gemke RJ, Broers CJ, van den Ende K, et al. Down syndrome: a novel risk factor for respiratory syncytial virus bronchiolitis—a prospective birth-cohort study. *Pediatrics* 2007;120(4):e1076-e81.
167. Katon WJ, Richardson L, Lozano P, McCauley E. The relationship of asthma and anxiety disorders. *Psychosomatic Medicine* 2004;66(3):349-55.
168. Nafstad P, Jaakkola J, Hagen J, Botten G, Kongerud J. Breastfeeding, maternal smoking and lower respiratory tract infections. *European Respiratory Journal* 1996;9(12):2623-9.
169. Cushing AH, Samet JM, Lambert WE, Skipper BJ, Hunt WC, Young SA, et al. Breastfeeding reduces risk of respiratory illness in infants. *American journal of epidemiology* 1998;147(9):863-70.
170. Martinez FD. Development of wheezing disorders and asthma in preschool children. *Pediatrics* 2002;109(Supplement E1):362-7.
171. Upton MN, McConnachie A, McSharry C, Hart CL, Smith GD, Gillis CR, et al. Intergenerational 20 year trends in the prevalence of asthma and hay fever in adults: the Midspan family study surveys of parents and offspring. *BMJ* 2000;321(7253):88-92.
172. Patel MX, Doku V, Tennakoon L. Challenges in recruitment of research participants. *Advances in Psychiatric Treatment* 2003;9(3):229-38.
173. Attfeld MD. Respiratory Questionnaires.



174. *Living with Asthma Questionnaire*  
<http://www.psy.plymouth.ac.uk/research/mhyland/Scoring%20%20th e%20Living%20with%20Asthma.pdf> (accessed).
175. The English Indices of Deprivation 2010.
176. Association WM. Declaration of Helsinki. *Ethical Principles for Medical Research Involving Human Subjects* 2008.  
<http://www.wma.net/en/30publications/10policies/b3/>.
177. Association WM. Ethics and Medical Research. Medical Ethics Manual. World Medical Association; 2009.
178. Barrett B, Locken K, Maberry R, Schwamman J, Brown R, Bobula J, et al. The Wisconsin Upper Respiratory Symptom Survey (WURSS): a new research instrument for assessing the common cold. *J Fam Pract* 2002;51(3):265.
179. Statistics OoN. Introduction to collecting data on ethnic group, religion and national identity. *Guidance and Methodology* 2013.  
<http://www.ons.gov.uk/ons/guide-method/measuring-equality/equality/ethnic-nat-identity-religion/guide--measuring-equality/index.html>.
180. Donnelley R. Collecting Equality Information. Guidance on Asking Questions on Ethnic Groups. Analysis SJ. Scottish Government; 2012.
181. Commission EaHR. Ethnic Monitoring: A Guide for Public Authorities. 2012.  
[http://www.equalityhumanrights.com/uploaded\\_files/PSD/12\\_ethnic\\_monitoring.pdf](http://www.equalityhumanrights.com/uploaded_files/PSD/12_ethnic_monitoring.pdf).
182. Authority HR. Applying for ethical review. *NRES FAQs* 2013;2013.
183. Morton LM, Cahill J, Hartge P. Reporting Participation in Epidemiologic Studies: A Survey of Practice. *American Journal of Epidemiology* 2006;163(3):197-203.
184. Gelder MMv, Bretveld RW, Roeleveld N. Web-based questionnaires: the future in epidemiology? *Am J Epidemiol* 2010;172(11):1292-8.
185. Smith B, Smith TC, Gray GC, Ryan MAK. When Epidemiology Meets the Internet: Web-based Surveys in the Millennium Cohort Study. *American Journal of Epidemiology* 2007;166(11):1345-54.
186. Smith B, Smith TC, Gray GC, Ryan MAK. When Epidemiology Meets the Internet: Web-based Surveys in the Millennium Cohort Study. *American Journal of Epidemiology* 2007;166(11):1345-54.
187. Mavis BE, Brocato JJ. Postal surveys versus electronic mail surveys. The tortoise and the hare revisited. *Eval Health Prof* 1998;21(3):395-408.
188. Leece P, Bhandari M, Sprague S, Swiontkowski MF, Schemitsch EH, Tornetta P, et al. Internet versus mailed questionnaires: a controlled comparison (2). *J Med Internet Res* 2004;6(4):e39.
189. Atherton H, Oakeshott P, Aghaizu A, Hay P, Kerry S. Use of an online questionnaire for follow-up of young female students recruited to a randomised controlled trial of chlamydia screening. *J Epidemiol Community Health* 2010;64(7):580-4.
190. Fleming CM, Bowden M. Web-based surveys as an alternative to traditional mail methods. *J Environ Manage* 2009;90(1):284-92.
191. Mayr A, Gefeller O, Prokosch HU, Pirkl A, Frohlich A, de Zwaan M. Web-based data collection yielded an additional response bias--but

- had no direct effect on outcome scales. *J Clin Epidemiol* 2012;65(9):970-7.
192. Callas PW, Solomon LJ, Hughes JR, Livingston AE. The influence of response mode on study results: offering cigarette smokers a choice of postal or online completion of a survey. *J Med Internet Res* 2010;12(4):e46.
  193. Van Selm M, Jankowski NW. Conducting Online Surveys. *Quality and Quantity* 2006;40(3):435-56.
  194. Rolfson O, Salomonsson R, Dahlberg LE, Garellick G. Internet-based follow-up questionnaire for measuring patient-reported outcome after total hip replacement surgery-reliability and response rate. *Value Health* 2011;14(2):316-21.
  195. Russell CW, Boggs DA, Palmer JR, Rosenberg L. Use of a web-based questionnaire in the Black Women's Health Study. *Am J Epidemiol* 2010;172(11):1286-91.
  196. Smith AB, King M, Butow P, Olver I. A comparison of data quality and practicality of online versus postal questionnaires in a sample of testicular cancer survivors. *Psychooncology* 2013;22(1):233-7.
  197. Braithwaite D, Emery J, De Lusignan S, Sutton S. Using the Internet to conduct surveys of health professionals: a valid alternative? *Fam Pract* 2003;20(5):545-51.
  198. Manfreda KL, Batagelj Z, Vehovar V. Design of Web Survey Questionnaires: Three Basic Experiments. *Journal of Computer-Mediated Communication* 2002;7(3):0-.
  199. Derby DC, Haan A, Wood K. Data quality assurance: an analysis of patient non-response. *Int J Health Care Qual Assur* 2011;24(3):198-210.
  200. Ritter P, Lorig K, Laurent D, Matthews K. Internet versus mailed questionnaires: a randomized comparison. *J Med Internet Res* 2004;6(3):e29.
  201. Cooksey R, Brophy S, Husain MJ, Irvine E, Davies H, Siebert S. The information needs of people living with ankylosing spondylitis: a questionnaire survey. *BMC Musculoskelet Disord* 2012;13:243.
  202. Lusk C, Delclos GL, Burau K, Drawhorn DD, Aday LA. Mail versus internet surveys: determinants of method of response preferences among health professionals. *Eval Health Prof* 2007;30(2):186-201.
  203. Danon L, Read JM, House TA, Vernon MC, Keeling MJ. Social encounter networks: characterizing Great Britain. *Proceedings of the Royal Society B: Biological Sciences* 2013;280(1765).
  204. McCabe SE, Diez A, Boyd CJ, Nelson TF, Weitzman ER. Comparing web and mail responses in a mixed mode survey in college alcohol use research. *Addict Behav* 2006;31(9):1619-27.
  205. Zuidgeest M, Hendriks M, Koopman L, Spreeuwenberg P, Rademakers J. A comparison of a postal survey and mixed-mode survey using a questionnaire on patients' experiences with breast care. *J Med Internet Res* 2011;13(3):e68.
  206. Beebe TJ, Locke GR, 3rd, Barnes SA, Davern ME, Anderson KJ. Mixing web and mail methods in a survey of physicians. *Health Serv Res* 2007;42(3 Pt 1):1219-34.

207. Wilson PM, Petticrew M, Calnan M, Nazareth I. Effects of a financial incentive on health researchers' response to an online survey: a randomized controlled trial. *J Med Internet Res* 2010;12(2):e13.
208. Elisabeth Deutsdens KdR, Martin Wetzels, Paul Oosterveld. Response Rate and Response Quality of Internet-Based Surveys: An Experimental Study. 2004.
209. Hunter J, Corcoran K, Leeder S, Phelps K. Is it time to abandon paper? The use of emails and the Internet for health services research - a cost-effectiveness and qualitative study. *J Eval Clin Pract* 2012.
210. Dykema J, Stevenson J, Klein L, Kim Y, Day B. Effects of E-Mailed Versus Mailed Invitations and Incentives on Response Rates, Data Quality, and Costs in a Web Survey of University Faculty. *Social Science Computer Review* 2012.
211. Balter KA, Balter O, Fondell E, Lagerros YT. Web-based and mailed questionnaires: a comparison of response rates and compliance. *Epidemiology* 2005;16(4):577-9.
212. Kongsved SM, Basnov M, Holm-Christensen K, Hjollund NH. Response rate and completeness of questionnaires: a randomized study of Internet versus paper-and-pencil versions. *J Med Internet Res* 2007;9(3):e25.
213. Classapps an Atomic Design LLCC. ASP Survey Software, SelectSurvey.Net(TM),Features. 2008;2013.
214. FormsCentral A. Create forms, online form creator | Adobe FormsCentral. *Features* 2013;2013.
215. Kirsch ST. Secure, convenient and efficient system and method of performing trans-internet purchase transactions. Google Patents; 1999.
216. Hawkins S, Yen DC, Chou DC. Awareness and challenges of Internet security. *Information Management & Computer Security* 2000;8(3):131-43.
217. Nosek BA, Banaji MR, Greenwald AG. E-Research: Ethics, Security, Design, and Control in Psychological Research on the Internet. *Journal of Social Issues* 2002;58(1):161-76.
218. Demchenko Y, Gommans L, de Laat C, Oudenaarde B. *Proceedings of the 6th IEEE/ACM International Workshop on Grid Computing*, 2005
219. Treweek S, Barnett K, MacLennan G, Bonetti D, Eccles MP, Francis JJ, et al. E-mail invitations to general practitioners were as effective as postal invitations and were more efficient. *J Clin Epidemiol* 2012;65(7):793-7.
220. MailChimp Blog. *Fast list Signups on Mobile QR codes*. Weblog. <http://blog.mailchimp.com/fast-list-signups-on-mobile-devices-with-qr-codes/> (accessed 2013).
221. MailChimp. Email Marketing Features Overview. 2013;2013.
222. MailChimp. Security FAQ. 2013;2013.
223. MailChimp. Resources | Spam Lawsuits. 2013;2013.
224. MailChimp. Avoiding the spam filters. *Support* 2011;2013.
225. MailChimp. *Features | Inbox Inspector*. 2013. <http://mailchimp.com/features/inbox-inspector/> (accessed.

226. Secretary of State G, UK. Electronic Communications: The Privacy and Electronic Communications (EC Directive) Regulations 2003. Archives TN. 2426. legalisation.gov.uk: Crown; 2003.
227. Couper MP. Web Surveys: the Good, the Bad and the Ugly. *Unpublished manuscript (Paper submitted to Public Opinion Quarterly)* 2000.
228. Tedesco.H ZALNEM. Designing Surveys for the Next Millennium: Web-based Questionnaire Design Issues - WebSM. In: The ASC's 3rd International Conference on Survey and Statistical Computing, 1999: Leading Survey and Statistical Computing into the New Millennium, 1999.
229. Vehovar V, Manfreda KL, Batagelj Z, Center C. *Proceedings of the American Statistical Association, Survey Research Methods Section*, 2000
230. Dillman DABD. The Web Questionnaire Challenge to Survey Methodologists - WebSM. 2001. <http://www.websm.org/db/12/1162/rec/>.
231. Schleyer TKL, Forrest JL. Methods for the Design and Administration of Web-based Surveys. *Journal of the American Medical Informatics Association* 2000;7(4):416-25.
232. Gräf L. Assessing internet questionnaires: The online pretest lab. *Online social sciences* 2002;49-68.
233. SurveyMonkey. SurveyMonkey Audience Tips- Question Design Tips. 2013;2012.
234. Kwak N, Radler B. A comparison between mail and web surveys: Response pattern, respondent profile, and data quality. *JOURNAL OF OFFICIAL STATISTICS-STOCKHOLM-* 2002;18(2):257-74.
235. Eysenbach G, Wyatt J. Using the Internet for surveys and health research. *J Med Internet Res* 2002;4(2):E13.
236. Dillman DA, Bowker DK. The Web questionnaire challenge to survey methodologists. 2001.
237. Lumsden J. Online-questionnaire design guidelines. *RA Reynolds, R. Woods, & JD Baker, Electronic Surveys and Measurements* 2007:44-64.
238. Agency EP. *Guidance for Conducting Remedial Investigations and Feasibility Studies Under CERCLA*. US: Environmental Protection Agency, 1988 October.
239. Arain M, Campbell MJ, Cooper CL, Lancaster GA. What is a pilot or feasibility study? A review of current practice and editorial policy. *BMC Medical Research Methodology* 2010;10:67.
240. Thabane L, Ma J, Chu R, Cheng J, Ismaila A, Rios L, et al. A tutorial on pilot studies: the what, why and how. *BMC medical research methodology* 2010;10(1):1.
241. Arnold DM, Burns KE, Adhikari NK, Kho ME, Meade MO, Cook DJ. The design and interpretation of pilot trials in clinical research in critical care. *Crit Care Med* 2009;37(1 Suppl):S69-74.
242. Council MR. *MRC Guidance on managing risk in public health research*. MRC Data and Tissues Toolkit: Medical Research Council, 2011.

243. Hanley B, Truesdale A, King A, Elbourne D, Chalmers I. Involving consumers in designing, conducting, and interpreting randomised controlled trials: questionnaire survey. *BMJ* 2001;322(7285):519-23.
244. Staley K. *Exploring impact public involvement in NHS, public health and social care research*. 2009.  
<http://www.invo.org.uk/pdfs/Involve%5FExploring%5FImpactfinal28.10.09.pdf> (accessed April).
245. Van Teijlingen ER, Rennie A-M, Hundley V, Graham W. The importance of conducting and reporting pilot studies: the example of the Scottish Births Survey. *Journal of Advanced Nursing* 2001;34(3):289-95.
246. Committee HoCH. *Patient and Public Involvement in the NHS*. London: House of Commons, 2007 22 March.
247. Boynton PM, Greenhalgh T. Selecting, designing, and developing your questionnaire. *BMJ* 2004;328(7451):1312-5.
248. Tourangeau R, Couper MP, Conrad F. Spacing, Position, and Order: Interpretive Heuristics for Visual Features of Survey Questions. *Public Opinion Quarterly* 2004;68(3):368-93.
249. McColl E, Jacoby A, Thomas L, Soutter J, Bamford C, Steen N, et al. Design and use of questionnaires: a review of best practice applicable to surveys of health service staff and patients. *Health Technol Assess* 2001;5(31):1-256.
250. Edwards P. Questionnaires in clinical trials: guidelines for optimal design and administration. *Trials* 2010;11:2.
251. Stoutenborough JW. Demographic measures. In: Lavrakas PJ, ed. *The SAGE Encyclopedia of Social Science Research Methods, Volume 1*. Thousand Oaks, California, USA: SAGE Publications, Inc, 2004.  
[http://books.google.co.uk/books/about/The\\_SAGE\\_Encyclopedia\\_of\\_Social\\_Science.html?id=AB\\_JIZN-3j0C](http://books.google.co.uk/books/about/The_SAGE_Encyclopedia_of_Social_Science.html?id=AB_JIZN-3j0C).
252. Leung W-C. Student BMJ: How to design a questionnaire. *Education* 2001;09:171-216. <http://student.bmj.com/student/view-article.html?id=sbmj0106187>.
253. Teclaw R, Price MC, Osatuke K. Demographic Question Placement: Effect on Item Response Rates and Means of a Veterans Health Administration Survey. *Journal of Business and Psychology* 2012;27(3):281-90.
254. Nieuwenhuijsen MJ. Design of exposure questionnaires for epidemiological studies. *Occupational and Environmental Medicine* 2005;62(4):272-80.
255. Boynton PM, Greenhalgh T. Selecting, designing, and developing your questionnaire. *BMJ* 2004;328(7451):1312-5.
256. Stewart D, Wilson R, Selby P, Darbyshire J. Patient and public involvement. *Annals of Oncology* 2011;22(Suppl 7):vii54-vii6.
257. Health Do. Patient and Public Involvement. *Policy Research Programme* 2013;2013.
258. Research NifHa. Patient and Public Involvement (PPI) | PPI - Information for researchers. *Comprehensive Clinical Research* 2013;2013.
259. NICE. Patient and public involvement. 2007;2013.



260. Smith E, Ross F, Donovan S, Manthorpe J, Brearley S, Sitzia J, et al. Service user involvement in nursing, midwifery and health visiting research: a review of evidence and practice. *Int J Nurs Stud* 2008;45(2):298-315.
261. Kaplowitz MD, Lupi F, Couper MP, Thorp L. The Effect of Invitation Design on Web Survey Response Rates. *Social Science Computer Review* 2012;30(3):339-49.
262. Vigilante MS, Wogalter WJ. Effects of label format on knowledge acquisition and perceived readability by younger and older adults. *Ergonomics* 2003;46(4):327-44.
263. Statistics OfN. *Birth statistics, England and Wales (Series FM1) - No. 37, 2008*. Office for National Statistics, 2009.
264. Preacher KJ. *Calculation for the chi-square test: An interactive calculation tool for chi-square tests of goodness of fit and independence*. 2013. Available from: <http://quantpsy.org>. (accessed July 2013).
265. Statistics N. Resident Population Estimates by Ethnic Group. Statistics OoN. Office of National Statistics; 2009.
266. Kurmi OP, Semple S, Simkhada P, Smith WCS, Ayres JG. COPD and chronic bronchitis risk of indoor air pollution from solid fuel: a systematic review and meta-analysis. *Thorax* 2010;65(3):221-8.
267. Bausewein C, Jolley C, Moxham J, Reilly C, Lobo P, Kelly J, et al. Development, effectiveness and cost-effectiveness of a new out-patient Breathlessness Support Service: study protocol of a phase III fast-track randomised controlled trial. In: *BMC Pulm Med*. England, 2012:58.
268. Koshy G, Akrouf KA, Kelly Y, Delpisheh A, Brabin BJ. Asthma in Children in Relation to Pre-term Birth and Fetal Growth Restriction. *Matern Child Health J* 2012.
269. Marmot M. Social determinants of health inequalities. *The Lancet* 2005;365(9464):1099-104.
270. Research NIfH. *The NIHR Carbon Reduction Guidelines*. NHS National Institute for Health Research, October 2010.
271. Smith AB, King M, Butow P, Olver I. A comparison of data quality and practicality of online versus postal questionnaires in a sample of testicular cancer survivors. *Psychooncology* 2013;22(1):233-7.
272. Pizzi C, De Stavola BL, Pearce N, Lazzarato F, Ghiotti P, Merletti F, et al. Selection bias and patterns of confounding in cohort studies: the case of the NINFEA web-based birth cohort. *J Epidemiol Community Health* 2012;66(11):976-81.
273. Katusic SK, Colligan RC, Barbaresi WJ, Schaid DJ, Jacobsen SJ. Potential influence of migration bias in birth cohort studies. *Mayo Clin Proc* 1998;73(11):1053-61.
274. Lucas PJ, Allnock D, Jessiman T. How are European birth-cohort studies engaging and consulting with young cohort members? *BMC Med Res Methodol* 2013;13:56.
275. Lea W. *Identity Guidelines*. National Institute for Health Research, 2012 June 2012.
276. Flesch R. A new readability yardstick. *Journal of applied psychology* 1948;32(3):221.

277. Klare GR. Assessing readability. *Reading research quarterly* 1974;62-102.
278. Sticht TG. *Reading for working: A functional literacy anthology*: HumRRO, 1975.
279. Sedgwick P. Internal and external validity. *BMJ* 2010;340.
280. Bland JM, Altman DG. Statistics notes: Cronbach's alpha. *Bmj* 1997;314(7080):572.
281. Sijtsma K. On the use, the misuse, and the very limited usefulness of Cronbach's alpha. *Psychometrika* 2009;74(1):107-20.
282. Food U. Drug Administration: Guidance for industry: Patient-reported outcome measures—Use in medical product development to support labeling claims. *Federal Register* 2009;235(74):65132-3.

# Appendix



## Appendix 1: Literature Review Tables

**Table 8.1: Summary of Birth Cohort Studies**

Study Name	Abbreviation	Year	Country/ Region	Type	No. Participants
National Survey of Health and Development	NSHD	1946	United Kingdom	National	5,362
National Child Development Survey	NCDS	1958	United Kingdom	National	17,416
1970 British Cohort Study	BCS70	1970	United Kingdom	National	16,571
Aberdeen Children of the 1950s study	-	1950	Aberdeen, UK	Regional	12,150
Avon Longitudinal Study of Parents and Children	ALSPAC	1991	Bristol, UK	Regional	13,761
Isle of Man Birth Cohort Study	-	1991	Isle of Man, UK	Regional	1,314
Born in Bradford	BiB	2007	Bradford, UK	Regional	13, 776
European Longitudinal Study of Pregnancy and Childhood	ELSPAC	1991	Europe	International	~40,000
Generation R	-	2002	Netherlands	National	9,778
All Babies in Southeast Sweden	ABIS	1997	Sweden	Regional	17,055
National Children's Study of Environmental effects on Child Health and Development	-	2007	United States of America	National	~100,000
Dunedin Multidisciplinary Health and Development Study	-	1972	Dunedin, New Zealand	Regional	1037
Mater University of Queensland Study of Pregnancy and its outcomes	MUSP	1981	Mater, Australia	Regional	7,223
Amsterdam Born Children and their Development	ABCD	2003	Amsterdam, Netherlands	Regional	6,161
Danish National Birth Cohort	-	1996	Denmark	National	91,256
Norwegian Mother and Child Birth Cohort Study	MoBa	1997	Norway	National	64,136
Pelotas Birth Cohort Study		1982	Pelotas, Brazil	Regional	5,914

**Table 8 2: Summary of Adults Respiratory Questionnaires**

<b>Name</b>	<b>Abbreviation</b>	<b>Completion</b>	<b>Respiratory condition/Symptoms</b>
St George's Respiratory Questionnaire	SQRQ	Self-completion	Asthma, Chronic Airflow Limitation and Bronchiectasis
Wisconsin Upper Respiratory Questionnaire	WVRSS44	Self-completion	Common cold
Leicester cough Questionnaire	LCQ	Self-completion	Chronic cough
Pneumoconiosis Field Research Respiratory Symptom Questionnaire	PFR	Self-completion	Pneumoconiosis
Questionnaire used in the Obstructive Lung Disease in Northern Sweden study	OLINq	Self-completion	Asthma, allergy, chronic bronchitis, and chronic obstructive pulmonary disease
Respiratory and Allergy Focused questionnaire	OLIN + GA2LEN	Self-completion	Asthma and allergic disease
American Thoracic Society and Division of Lung Diseases Questionnaire	ATS DLD 78	Self-completion	Asthma and allergic disease
Global Allergy and Asthma European Network Questionnaire	GA2LENq	Self-completion	Asthma, allergic disease and rhinitis
Cystic Fibrosis Questionnaire Revised	CFQ-R	Self-completion, proxy or interview	Cystic Fibrosis
Cystic Fibrosis Questionnaire Revised	CFQ-R	Self-completion, proxy or interview	Cystic Fibrosis
Leicester Cough Questionnaire	LCQ	Self-completion	Chronic cough and impact on quality of life
Cough Quality of Life Questionnaire	CQLQ	Self-completion	Impact of acute, chronic and smokers cough
Medical Research Council's Questionnaire on Respiratory Symptoms	MRC RQ	Self-completion or Interview	Asthma, bronchitis
Medical Research Council's Committee on Environmental and Occupational Health Questionnaire on respiratory symptoms,	MRC EO	Self-completion or Interview	Environmental and occupational respiratory symptoms
Shortness of breath questionnaire	UCSD	Self-completion	Pulmonary Fibrosis
Chronic Respiratory Questionnaire	CRQ	Interview administered	Chronic Obstructive Pulmonary Disease
Chronic Respiratory Questionnaire-Self Reported	CRQ SR	Self-completion	Chronic Obstructive Pulmonary Disease
Jackson Cold Scale	JCS	Self-completion or Interview	Coryzal symptom
Orebro Indoor Climate Questionnaire	MM40	Self-completion	Respiratory symptoms relating to indoor air problems
New Finnish Respiratory Questionnaire	-	Self-completion	Asthma, allergic rhinitis and conjunctivitis
Tuohilampi Questionnaire	-	Self-completion	Asthma, allergic rhinitis and conjunctivitis
Breathlessness, Cough and Sputum Scale	BCSS	Self-completion	Chronic Obstructive Pulmonary Disease
Integrated Therapeutics Group Asthma Short Form	ITG-ASF	Self-completion	Asthma
Environmental Symptom Questionnaire	ESQ	Self-completion	Symptoms produced by exposure to several different climatic conditions
European Community Respiratory Health Survey Questionnaire	ECRHSq	Self-completion or Interview	Respiratory symptoms, including asthma-like symptoms, COPD
Nijmegen Questionnaire	NQ	Self-completion	Symptoms associated with dysfunctional breathing patterns particularly hyperventilation syndrome



<b>Name</b>	<b>Abbreviation</b>	<b>Completion</b>	<b>Respiratory condition/Symptoms</b>
Asthma Quality of Life Questionnaire (juniper et al)	AQLQ	Self-completion or Interview	Asthma specific
International Union against Tuberculosis and Lung Disease Bronchial Symptoms Questionnaire	IUATLD	Self-completion or Interview	Tuberculosis and bronchial symptoms
Symptom Self Reporting Inventory	SCL-90	Self-completion	Psychiatric
Living with Asthma questionnaire	LivAQ	Self-completion or Interview	Asthma only
Questionnaire of the European Community for Coal and Steel on respiratory symptoms	ECCS	Self-completion	Chronic bronchitis and emphysema
Adult questionnaire used in the Arizona Tucson Epidemiologic Study of Obstructive Lung Diseases	-	Self-completion	Obstructive Lung Disease
Questionnaire used in the investigation into the occurrence of allergies, asthma and other lung diseases in Hordaland	-	Self-completion	Asthma, Bronchitis and allergies
Questionnaire used in the Cooperative European Anti-Smoking Evaluation (CEASE) trial,	CEASEq	Self-completion	Detailed tobacco use and exposure to tobacco history
Tasmanian Asthma Survey Questionnaire	TAHSq	Self-completion	Asthma, rhinitis, eczema and respiratory symptoms relating to outdoor wood smoke
Asthma Control Questionnaire	ACQ	Self-completion	Asthma
Integrated Therapeutics Group Asthma Short Form	ITG-ASF	Self-completion	Asthma specific health related quality of life

**Table 8 3: Summary of Paediatric Respiratory Questionnaires**

<b>Name</b>	<b>Abbreviation</b>	<b>Completion</b>	<b>Age (years)</b>	<b>Respiratory Disease/Symptoms</b>
Test for Respiratory and Asthma Control in Kids	TRACK	Care-giver completed	<5	Asthma
Paediatric Asthma Quality of Life Questionnaire	PAQLQ	Parental Completed	7-17	Asthma
American Thoracic Society children's questionnaire	ATS- DLD-78C	Parental Completed		Asthma, bronchitis
Asthma Control Questionnaire	ACQ	Parental Completed	6-16	Asthma
Cystic Fibrosis Questionnaire Revised	CFQ-R	Parental or Child completed	6-13	Cystic Fibrosis
Parent completed respiratory questionnaire for 1 year olds	-	Parental Completed	1-2	Wheeze and other respiratory symptoms
Jackson Cold Scale	JCS	Parental Completed	2-11	Coryzal symptom
International Study of Asthma and Allergies in Childhood Questionnaire	ISAACq	Parental or Child completed	6-7	Asthma and allergic disease
International Study of Asthma and Allergies in Childhood Questionnaire	ISAACq	Child completion	13-14	Asthma and allergic disease
Questionnaire used in the Pollution Effects on Asthmatic Children in Europe (PEACE) study	PEACEq	Parental Completed	6-12	Effects of air pollution upon respiratory symptoms and asthma
Liverpool Respiratory Symptom Questionnaire	LRSQ	Parental Completed	<5	Asthma, Cystic Fibrosis, Bronchiolitis
Respiratory questionnaire for 1-5 year olds	-	Parental Completed	1-5	Asthma, bronchiolitis
Wythenshawe Community Asthma Project Questionnaire	WYCAPq	Interview administered	1-4	Asthma
Integrated Therapeutics Group Child Asthma Short Form	ITG-CASF	Parental Completed	5-12	Symptoms and disability of chronic asthma
Boston respiratory questionnaire		Trained research assistant administered		Not yet validated in preschool population

## Appendix 2: IRAS Application Documentation

Figure 8.1: Power point presentation mock up of proposed online documentation



# IRAS Application supplementary documents


## The Liverpool Respiratory Birth Cohort Study

Patient Information, Consent form, Demographic and Exposures questionnaire and the LRSQ as will appear via Email and Online.


The Research Team: Rosanna Pickles, Professor Ben Shaw, Dr Kevin Southern, Dr Calum Semple

Date 10/02/12 - Version 1.0

---



INVITE EMAIL



Dear Parent,

**THANK YOU FOR YOUR INTEREST !**

Before leaving the Liverpool Women's Hospital you agreed to be contacted for a research study.

**The Liverpool Respiratory Birth Cohort Study** will study the respiratory symptoms (colds, wheezing, coughing and difficulty breathing) of children born in Liverpool from birth to the age of five years.

- We will send you a questionnaire, twice a year, for five years.
- This should take no more than 10 minutes to fill out.
- Your decision to participate will not affect your future care.
- All responses and details are handled in confidence.
- You can choose to leave the study at any stage

If you want to find out more please click here.  
You are not committing yourself to participate in the study at this stage.

If you do not wish to participate please click here.  
We will not send you any further emails regarding the study.  
Your decision not to take part will not affect your future care.

Thank you,

The Research Team

Miss Rosanna Pickles	MPhil student at the Institute of Translational Medicine
Dr Calum Semple	Senior Lecturer in Child Health and Respiratory Paediatric Clinician
Dr Kevin Southern	Reader in Respiratory and Neonatal Paediatrics
Professor Ben Shaw	Consultant in Respiratory and Neonatal Paediatrics

Date 10/02/12 - Version 1.0

ON THIS PAGE WE ARE ASKING YOU CONSENT TO TAKE PART IN

The Liverpool Respiratory Birth Cohort Study

**Why are we doing this?** We want to find out more about the respiratory symptoms, such as wheezing, coughing, that your child experiences and their effect on you and your family. We want to understand how these symptoms change over time and what makes them more or less likely to occur.

**Why have I been chosen?**

We are asking all parents of children born at the Liverpool Women's Hospital who were living within the L1-38 postcodes when their child was born. We are particularly interested in the Liverpool children's population as there are high levels of respiratory disease such as asthma and bronchiolitis.

**Do I have to take part?**

No, it is up to you to decide whether or not to take part. You are free to withdraw at any time, without giving a reason. You and your child's clinical care will not be affected if you do not wish to take part.

**What will it involve (before/during/after)?**

We ask you to complete a questionnaire about your child. We will email you a link to the questionnaire just twice a year for five years. The questionnaire should take no more than 10 minutes to complete. We will ask you a few questions about your family circumstances and your child's respiratory symptoms. We will keep you updated on how the study is running by email. At the end of the study we will send you a summary of the results for the whole study.

**Possible disadvantages of taking part**

We do not think there are any disadvantages to you or your child. All information is handled in strict confidence.

**Possible advantages of taking part**

Being involved in this study will not benefit you or your child directly. We hope the study will help children in the future by identifying what helps or worsens respiratory symptoms.

Click here if you have read enough and are happy to take part in the study

Click here if you would like to read more information or would like to contact the research team with a question.

Miss Rosanna Pickles *MPhil student at the Institute of Translational Medicine*  
Dr Calum Semple *Senior Lecturer in Child Health and Respiratory Paediatric Clinician*  
Dr Kevin Southern *Reader in Child Health and Respiratory Paediatric Clinician*  
Professor Ben Shaw *Consultant in Respiratory and Neonatal Paediatrics*

If you do not wish to participate please click here.  
We will not send you any further emails regarding the study.  
Your decision not to take part will not affect your future care.

Date 10/02/12 - Version 1.0

ON THIS PAGE WE ARE ASKING YOU CONSENT TO TAKE PART

IN The Liverpool Respiratory Birth Cohort Study

**Confidentiality and Data Protection**

All information collected about you and your child during the course of the research will be kept strictly confidential. All measures will be taken to ensure data is stored securely and your data will be kept anonymous Wherever possible.

**Communication with other NHS staff**

Your details will only be shared with the Liverpool Womens Hospital and Alder Hey Childrens Hospital which abide by strict guidelines for confidentiality.

**Publication**

No identifiable information will be included in any publications.

**What if there is a problem?**

Please contact members of the research team listed below if you encounter any problems.

Click here if you have read enough and are happy to take part in the study

Click here if you would like to read more information or would like to contact the research team with a question.

Miss Rosanna Pickles *MPhil student at the Institute of Translational Medicine*  
Dr Calum Semple *Senior Lecturer in Child Health and Respiratory Paediatric Clinician*  
Dr Kevin Southern *Senior Lecturer in Child Health and Respiratory Paediatric Clinician*  
Professor Ben Shaw *Consultant in Respiratory and Neonatal Paediatrics*

If you do not wish to participate please click here.  
We will not send you any further emails regarding the study.  
Your decision not to take part will not affect your future care.

Date 10/02/12 - Version 1.0

Current Contact Details

In subsequent polls, this page will also be presented with previous details with an option to update details where required.

Please enter: Mothers: Forename  Surname Fathers: Forename  Surname Baby's: Forename  Surname Address:  Postcode: Main email address: Home Telephone Number: Mobile Number: I would like to be contacted by:  

Date 10/02/12 - Version 1.0

*Note to parents you will only need to complete*1. Your Child's Date of Birth: day  month  year 2. Is your child:  3. What is the ethnicity of your child?: 

Date 10/02/12 - Version 1.0

## Demographics Questionnaire

*To be completed by the child's mother*

How many weeks pregnant were you when you gave birth?  weeks

How much did your child weigh at birth?  Pounds  Oz or  kg

Did you breast-feed [child's name]?

[conditional] How long did you breastfeed child's name for? Less than 1 month ☐ 1 to 3 months ☐ 4 months or more ☐

Did you smoke at any time during your pregnancy?

Did anybody else smoke in your house during your pregnancy?

What is your highest qualification?

Please select
Finished Secondary School, No Qualifications
GCSE's/ O levels
Vocational training
A levels
Diploma
Undergraduate Degree
Postgraduate degree

DROP DOWN MENU

*To be completed by either parent*

Does anyone in your house have any medical history of hay fever, asthma or eczema?

Date 10/02/12 - Version 1.0

## Exposure Questionnaire

**Note to reviewers: this form will be online using radio buttons and drop down menus. Sections will be presented conditionally. This questionnaire will be emailed 6 monthly in conjunction with the LRSQ**

Your previous contact details were:

I would like to be contacted by:

Have any of your contact details changed?

[conditional]

If so please complete as needed.

Address:

Postcode:

Main email address:

Home telephone number:

Mobile Number:

Date 10/02/12 - Version 1.0



*To be completed by either parent*

1. Does [child's name] attend nursery? Yes No
  2. Do you have any other children that live with you? Yes No
  3. Does [child's name] share a bedroom with anyone Yes No
- If yes, click following that apply: Parent or parents One other child two or more other children ?
4. Does any member of you household smoke at all? HELP *[conditional if yes]* Yes No  
i.e. someone that sleeps in the house or takes a meal in the house.
  5. Where do these people smoke ? tick all that apply
- Inside home Outside of home In car Indoor at at another location e.g. work or social

Date 10/02/12 - Version 1.0

*To be completed by either parent*

6. Does your child have any of the chronic health conditions, please select? *[conditional radio buttons if yes free text box appears to specify]* ? Yes No
  - Chronic/long term Chest diseases ? Yes No
  - Chronic/long term Heart diseases ? Yes No
  - Chronic/long term Kidney / Renal diseases ? Yes No
  - Chronic Neurological disease ? Yes No
  - Other chronic diseases ? Yes No
  - Diabetes? Yes No
  - Other ? Yes No
7. In the last 3 months how many times has your child seen your GP because of his/her chest? Yes No
  8. a) In the last 3 months has your child been to hospital because of his/her chest? Yes No
  - b) If yes how many times has your child been to hospital because of his/her chest?
- 1 time 2 times 3 times 4 times 5 times more than 5 times

Date 10/02/12 - Version 1.0

**1. This first question refers to at any time in your child's life:**

Has your child ever had wheezing (whistling noise coming from the chest) at any time in the past?

Please select
Yes
No

}] DROP DOWN MENU

**2. The next questions are specifically aimed at the last three months:**

**A) During the day (when awake) in the last three months:**

i) My child has had wheezing (whistling noise coming from the chest):

Please select
Every day
most days
some days
a few days
not at all

} DROP DOWN MENU

ii) My child has had a cough: Please select

← DROP DOWN MENU  
THE SAME AS  
DEMONSTRATED

iii) My child has had a rattly chest: Please select

iv) My child has been short of breath: Please select

Date 10/02/12 - Version 1.0

**B) During the night (when asleep) in the last three months :**

i) My child has had wheezing (whistling noise coming from the chest ):

Please select
Every day
most days
some days
a few days
not at all

ii) My child has had a cough: Please select

← DROP DOWN MENU

iii) My child has had a rattly chest: Please select

iv) My child has been short of breath: Please select

v) My child has snored : Please select

Date 10/02/12 - Version 1.0

3. How many colds has your child had in the last three months:

Please select

If the answer to the above question is 'none' continue to questions 5.

## Section D:

4. When my child has had a COLD in the last three months [conditional of positive response to Q3] :

a. My child has had wheezing (whistling noise coming from the chest):

b. My child has had a cough:

Please select

c. My child has had a rattly chest:

Please select

d. My child has been short of breath:

Please select

Please select  
Every day  
most days  
some days  
a few days  
not at all

DROP DOWN MENU

Date 10/02/12 - Version 1.0

5. When my child does NOT have a COLD, in the last three months:

a. My child has had wheezing (whistling noise coming from the chest):

b. My child has had a cough:

Please select

c. My child has had a rattly chest:

Please select

d. My child has been short of breath:

Please select

Please select  
Every day  
most days  
some days  
a few days  
not at all

Date 10/02/12 - Version 1.0

6. These next three questions are about other problems your child may have had.

Over the last three months:

- a. My child has had noisy breathing that does not seem to come from the chest :
- b. My child has had fast breathing:
- c. My child has had noisy breathing that appears to come from the throat or back of the throat:

Date 10/02/12 - Version 1.0

7. The next four questions are on how your child's chest symptoms actually affect HIM or HER over the last three months:

- a. My child's chest symptoms have affected my child's feeding or eating:
- b. My child's chest symptoms have woken up my child:
- c. My child's chest symptoms have reduced my child's activity:
- d. My child's chest symptoms have made my child unusually tired:

Date 10/02/12 - Version 1.0

**8. The next four questions are on how your child's chest symptoms actually affect HIM or HER over the last three months:**

a. My child's chest symptoms have affected my child's feeding or eating:

Please select
Every day
most days
some days
a few days
not at all

b. My child's chest symptoms have woken up my child:

Please select

c. My child's chest symptoms have reduced my child's activity:

Please select

d. My child's chest symptoms have made my child unusually tired:

Please select

Date 10/02/12 - Version 1.0

**9. The next four questions are on how your child's chest symptoms actually affect YOU and YOUR family's life the last three months:**

a. My child's chest symptoms have limited my activities:

Please select

b. My child's chest symptoms have resulted in adjustments being made to our family life:

Please select

c. My child's chest symptoms have disturbed our sleep:


Please select

d. I have been worried about my child's chest symptoms:

Please select

Date 10/02/12 - Version 1.0

**Figure 8 2: Final Recruitment Postcard**




UNIVERSITY OF  
**LIVERPOOL**

Thank you for your interest in the....

## Liverpool Baby Breathing Study

The Liverpool Respiratory Birth Cohort Study



Liverpool Women's  
NHS Foundation Trust  
*Dedicated to you*

---


**The Liverpool Baby Breathing Study** will study the respiratory symptoms (colds, coughs, wheezing and breathing problems) of children born in Liverpool from when they are born until they are five years old.

**Why are we doing this?**  
We want to find out more about the respiratory symptoms, such as wheezing and coughing that your child experiences and their effect on your family. The aim of our study is to try to understand how these symptoms change over time and what makes them more or less likely to occur.

**Why have I been chosen?**  
We are asking all parents of children born at the Liverpool Women's Hospital who are living within the **L1-L38 postcodes only**, if they would like to take part. We are particularly interested in the children of Liverpool as there are high levels of respiratory diseases such as asthma and bronchiolitis.

**If you agree to take part:**

- We will send you a questionnaire online or by post twice a year, for five years
- The first questionnaire should take less than 10 minutes to complete
- Each follow-up questionnaire should take less than 5 minutes to complete
- Your decision to participate will not affect you or your child's future care in any way
- All responses and personal details will be handled in the strictest confidence
- You may choose to leave the study at any time





UNIVERSITY OF  
**LIVERPOOL**

Thank you for your interest in the....

## Liverpool Baby Breathing Study

The Liverpool Respiratory Birth Cohort Study



Liverpool Women's  
NHS Foundation Trust  
*Dedicated to you*

---

To register your interest in the **Liverpool Baby Breathing Study** simply fill in your details below, and give this card to a member of staff, or pop it in the collection box. Alternatively, you can enter your details online by scanning the QR code.

<b>Baby's First Name:</b> _____	<b>Last Name:</b> _____
<b>Baby's Date of Birth:</b> _____	<b>Singleton:</b> <input type="checkbox"/> <b>Twin:</b> <input type="checkbox"/> <b>Triplet:</b> <input type="checkbox"/>
<b>Mother's First Name:</b> _____	<b>Last Name:</b> _____
<b>Email:</b> _____	<b>Postcode:</b> L _____
<b>Main telephone number:</b> _____	<b>Please contact me by:</b> email <input type="checkbox"/> post <input type="checkbox"/>



**By providing these details I agree to be contacted by the Research team.**

Don't worry, you are not committing yourself to join the study at this stage!

We will contact you in four months time to confirm that you are still interested!

If you would like any further information, you can contact the research team directly by emailing [BabyStudy@liv.ac.uk](mailto:BabyStudy@liv.ac.uk) or calling (0151) 2824532.

Affix Hospital Label Here

Please scan this code using your QR reader



Table 8 3: Patient Poster



You are invited to participate in...

## The Liverpool Baby Breathing Study

The Liverpool Respiratory Birth Cohort Study

Have you recently had a baby here at Liverpool Women's?  
Do you live in a Liverpool post code (L1-L38)?

### The Liverpool Baby Breathing Study...

will study the respiratory symptoms (colds, coughs, wheezing and breathing problems) of children born in Liverpool from birth to the age of five years.

### Interested?

Ask for one of the sign-up **postcards** that are available on Jeffcoate ward, Matbase or the Neonatal unit.

OR

Scan this QR code using the instructions below and sign up using our online form!

Step 1 - Go to your app store on your smartphone and search for a "QR" or "Scanner".

Step 2 - Download the highest rated free QR scanner

Step 3 - Once downloaded, OPEN the app and follow the instructions. You will need to aim your camera at the QR code and scan/photograph the QR code

Step 4 - You'll be taken to the sign up form for the study- enter your details here to take part!!



Sign-up QR code



### What will it involve?

A short online or postal questionnaire, twice a year, for five years

### Why are we doing this?

We want to find out more about the respiratory symptoms that your child experiences and their affect on your family, how these symptoms change over time and what makes them more or less likely to occur.

### Questions?

If you would like further information, please email the research team at [BabyStudy@liverpool.ac.uk](mailto:BabyStudy@liverpool.ac.uk) or call (0151) 282 4532





**Figure 8.4: Postal Consent Form**



## Consent Form



**Title of Project:** [Liverpool Baby Breathing Study](#) (The Liverpool Respiratory Birth Cohort Study)

**Name of Researchers:**

Miss Rosanna Pickles, Miss Bethan Griffith, Dr Calum Semple, Dr Kevin Southern and Professor Ben Shaw

**Please tick box**

1. I confirm that I have read and understand the further information section dated 01/05/2013 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that our family and child's participation in the study is entirely voluntary and that we have the right to withdraw at any time without stating a reason and without affecting my care and my family's care in any way. ☐
3. I understand that the data collected by this study will be looked at by members of the research team named above and may be scrutinised by regulatory authorities or by the host NHS Trusts. ☐
4. I have read and understand the above consent form, I certify that I am the parent/guardian of the child recruited. ☐
5. I give permission for our family and my child to be involved in the above study. ☐

**Child's Forename (first/given name):** \_\_\_\_\_ **Surname:** \_\_\_\_\_

**Your Child's Date of birth:** Day: \_\_\_\_\_ Month: \_\_\_\_\_ Year : \_\_\_\_\_

**Mother's Forename (first/given name):** \_\_\_\_\_ **Surname:** \_\_\_\_\_

**Mothers Signature for Consent:** \_\_\_\_\_

**Today's Date:** Day: \_\_\_\_\_ Month: \_\_\_\_\_ Year : \_\_\_\_\_





**Figure 8.5: Original Patient Information Sheet Submitted to the NRES**  
(This document has since been formatted to feature at the beginning of the questionnaire. The online version provides an option button for mothers to select to read more information while the postal form includes the complete information.)



## **The Liverpool Respiratory Birth Cohort Study**

### **Patient**

#### **Why are we doing this?**

We would like to find out more about respiratory symptoms, such as wheezing, coughing, that your child experiences and their effect on you and your family. We want to understand how these symptoms change over time and what makes them more or less likely to occur.

#### **Why have I been chosen?**

We are asking all parents of children born at the Liverpool Woman's Hospital who were living within the L1-38 postcodes when their child was born. We are particularly interested in Liverpool children's population as there are high levels of respiratory diseases such as asthma and bronchiolitis.

#### **Do I have to take part?**

No, it is up to you to decide whether or not to take part. You are free to withdraw at any time, without giving a reason. You and your child's clinical care will not be affected if you do not wish to take part.

#### **What will it involve?**

We ask you to complete a questionnaire about your child. We will email you a link to the questionnaire just twice a year for five years. The questionnaire should take no more than 10 minutes to complete. We will ask you a few questions about your family circumstances and your child's respiratory symptoms.

We will keep you updated on how the study is running by email. At the end of the study we will send you a summary of the results for the whole study.

**Possible disadvantages of taking part**

We do not think there are any disadvantages to you or your child. All information is handled in strict confidence.

**Possible advantages of taking part**

Being involved in this study will not benefit you or your child directly. We hope the study will help children in the future by identifying what helps or worsens respiratory symptoms.

**Confidentiality and Data Protection**

All information collected about you and your child during the course of the research will be kept strictly confidential. All measures will be taken to ensure data is stored securely and your data will be kept anonymous wherever possible.

**Communication with other NHS staff**

Your details will only be shared with the Liverpool Women's Hospital and Alder Hey Children's Hospital which abide by strict guidelines for confidentiality.

**Publication**

No identifiable information will be included in any publications.

**What if there is a problem?**

Please contact members of the research team listed below if you encounter any problems.

**The Research Team**

Miss Rosanna Pickles	<i>MPhil student at the Institute of Translational Medicine</i>
Dr Calum Semple	<i>Senior Lecturer in Child Health and Respiratory Paediatric Clinician</i>
Dr Kevin Southern	<i>Senior Lecturer in Child Health and Respiratory Paediatric Clinician</i>
Professor Ben Shaw	<i>Consultant in Respiratory and Neonatal Paediatrics</i>

### Appendix 3: Summary of Articles Evaluating Online Questionnaires

**Table 8.4: Summary of Papers Evaluating Online Questionnaires**

Title	Year	Aim	Target Population	Age (years)
Postal surveys versus electronic mail surveys. The tortoise and the hare revisited.	1998	Postal vs Email Surveys	Professionals subscribed to a listserv dedicated to medical education	NK
Health surveys in the workplace: comparison of postal, email and World Wide Web methods.	1999	Postal vs Email and Online Survey vs Email Surveys Only	English University Staff	NK
The information needs of people living with Ankylosing Spondylitis: a questionnaire survey.	2012	Postal vs Online Questionnaire	Welsh Ankylosing Spondylitis patients	over 20
Web-based data collection yielded an additional response bias--but had no direct effect on outcome scales.	2012	Postal vs Online Questionnaire	Participants of the German Weight Control Registry	NK
Is it time to abandon paper? The use of emails and the Internet for health services research - a cost-effectiveness and qualitative study.	2012	Postal vs Email Invitations	Primary care patients	NK
A web-based computer-tailored smoking prevention programme for primary school children: intervention design and study protocol.	2012	Postal Intervention vs Emailed Intervention	Primary School Children	10-13
E-mail invitations to general practitioners were as effective as postal invitations and were more efficient.	2012	Postal vs Email Invitations	GP's	
A comparison of data quality and practicality of online versus postal questionnaires in a sample of testicular cancer survivors.	2013	Postal vs Online Questionnaire	Testicular Cancer Survivors	NK
A comparison of a postal survey and mixed-mode survey using a questionnaire on patients' experiences with breast care.	2011	Mixed Mode(Combining internet surveys with postal follow up)	Breast Care Patients	NK
Data quality assurance: an analysis of patient non-response.	2011	Paper vs Electronic Surveys	Chiropody patients	NK

<b>Title</b>	<b>Year</b>	<b>Aim</b>	<b>Target Population</b>	<b>Age (years)</b>
Internet-based follow-up questionnaire for measuring patient-reported outcome after total hip replacement surgery-reliability and response rate.	2011	Paper vs Online Questionnaire	Swedish Hip Arthroplasty Register	NK
Impact and costs of incentives to reduce attrition in online trials: two randomized controlled trials.	2011	Incentives and Post vs Online Surveys	Participants from Down Your Drink Pilot Trial	Mean age 37
The influence of response mode on study results: offering cigarette smokers a choice of postal or online completion of a survey.	2010	Paper vs Electronic Surveys	Cigarette smokers who intended to quit	NK
Use of a web-based questionnaire in the Black Women's Health Study.	2010	Postal vs Online Questionnaire: Utility and cost effectiveness	Participants of the Black Women's Health Study	21-69
Web-based questionnaires: the future in epidemiology?	2010	Review of advantages and disadvantages of web based questionnaires	N/A	N/A
Use of an online questionnaire for follow-up of young female students recruited to a randomised controlled trial of Chlamydia screening.	2010	Postal vs Online Questionnaire: Response rates	Female students taking part in a Chlamydia screening trial	16-27
College students' response rate to an incentivized combination of postal and web-based health survey.	2010	Paper vs Online Questionnaire	University students	Mean age 23
Questionnaires in clinical trials: guidelines for optimal design and administration.	2010	Evidence for questionnaire design	N/A	N/A
Combining web-based and mail surveys improve response rates: a PBRN study from PRIME Net.	2009	Paper vs Electronic Surveys	Clinicians	NK
Response rate and completeness of questionnaires: a randomized study of Internet versus paper-and-pencil versions.	2007	Paper vs Online Questionnaire	Women referred for a mammogram at a public Danish hospital	less than 67
Parents' attitudes towards hepatitis B vaccination for their children. A survey comparing paper and web questionnaires, Sweden 2005.	2005	Postal vs Online Questionnaire	Parents to a child born in 2002 in Sweden	NK
Mixing web and mail methods in a survey of physicians.	2007	Mixed Mode (two different methods)	Physicians with a Mayo Clinic Appointment	NK
Mail versus internet surveys: determinants of method of response preferences among health professionals.	2007	Postal vs Online Questionnaire: Response rates	Texan Healthcare Professionals	NK

<b>Title</b>	<b>Year</b>	<b>Aim</b>	<b>Target Population</b>	<b>Age (years)</b>
Feasibility of using web-based questionnaires in large population-based epidemiological studies.	2006	Paper vs Online Questionnaire	Women in Sweden	30-49
Comparing web and mail responses in a mixed mode survey in college alcohol use research.	2006	Mixed Mode	US college students	NK
Effects of survey mode on self-reports of adult alcohol consumption: a comparison of mail, web and telephone approaches.	2005	Postal vs Online Questionnaire vs Telephone Interview	NK	Aged 18 or older
Evaluating patients' experiences with individual physicians: a randomized trial of mail, internet, and interactive voice response telephone administration of surveys.	2006	Postal vs Online Questionnaire vs interactive voice response	Adult Patients	Mean age 56
Web-based and mailed questionnaires: a comparison of response rates and compliance.	2005	Paper vs Online Questionnaire	Swedish population	20-59
Internet versus mailed questionnaires: a controlled comparison (2).	2004	Paper vs Online Questionnaire	Members of the Orthopaedic Trauma Association	NK
Internet versus mailed questionnaires: a randomized comparison.	2004	Paper vs Online Questionnaire	Internet recruited subjects	10-89
Comparison of web and mail surveys in collecting illicit drug use data: a randomized experiment.	2004	Postal vs Online Questionnaire	US undergraduate students	NK
Using the Internet to conduct surveys of health professionals: a valid alternative?	2003	Systematic Review of Internet surveys of health professionals	N/A	N/A

## Appendix 4: Feasibility Studies Documentation

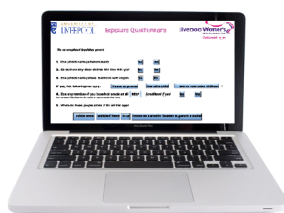
Figure 8.6: Documentation for PPI Interviews



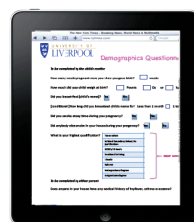
# Liverpool Respiratory Birth Cohort Study

Pilot

What would be the most convenient way for you to complete a questionnaire?



Laptop or PC



Tablet



Smart Phone

To which (if any) of these devices do you have access?

## Layout:

How do you prefer the information to be presented to you?

All the information/questions on one page?

A few similar questions grouped together over a few pages?

One question per page?



The LRSQ



1. This first question refers to at any time in your child's life:

Has your child ever had wheezing (whistling noise coming from the chest) at any time in the past?

Please select
Yes
No

2. The next questions are specifically aimed at the last three months:

A) During the day (when awake) in the last three months:

i) My child has had wheezing (whistling noise coming from the chest):

ii) My child has had a cough:

iii) My child has had a rattly chest:

iv) My child has been short of breath:

B) During the night (when asleep) in the last three months :

i) My child has had wheezing (whistling noise coming from the chest ):

ii) My child has had a cough:

iii) My child has had a rattly chest:

iv) My child has been short of breath:

v) My child has snored :

Next

Done: 37%

Densely filled so you can see all the questions?

1

**B) During the night (when asleep) in the last three months :**

i) My child has had wheezing (whistling noise coming from the chest ):

ii) My child has had a cough:

iii) My child has had a rattly chest:

iv) My child has been short of breath:

v) My child has snored :

**Next**

Done: 37%

**A few questions at a time so it's manageable?**

2

**7. The next four questions are on how your child's chest symptoms actually affect HIM or HER over the last three months:**

a. My child's chest symptoms have affected my child's feeding or eating:

Please select
Every day
most days
some days
a few days
not at all

**Next**

Done: 37%

**One question at a time so you can think properly about each one?**

3



## Format

### What kind of background appeals to you the most?

## Plain

## Images

Coloured

## Patterns

White

**Would you prefer a page to be colourful, or does a more neutral format appeal to you more?**



## The LRSQ



**B) During the night (when asleep) in the last three months :**

i) My child has had wheezing (whistling noise coming from the chest):

ii) My child has had a cough: Please select

iii) My child has had a rattly chest: Please selectiv) My child has been short of breath: Please select

v) My child has snored : Please select

1

....A plain and simple page with only the relevant text?

## The LRSQ

**B) During the night (when asleep) in the last three months :**

i) My child has had wheezing (whistling noise coming from the chest ):

ii) My child has had a cough:

iii) My child has had a rattly chest:

iv) My child has been short of breath:

v) My child has snored :

2a

....Quite plain but with a little colour in the background?

## The LRSQ

**B) During the night (when asleep) in the last three months :**

i) My child has had wheezing (whistling noise coming from the chest ):

ii) My child has had a cough:

iii) My child has had a rattly chest:

iv) My child has been short of breath:

v) My child has snored :

2b

A tiny bit of colour?

## Liverpool Respiratory Symptom Questionnaire

6. These next three questions are about other problems your child may have had.

Over the last three months:

- a. My child has had noisy breathing that does not seem to come from the chest :
- b. My child has had fast breathing:
- c. My child has had noisy breathing that appears to come from the throat or back of the throat:

3

NEXT

Plain but with different or unusual fonts?

Progress

32 %

## Themes, Images and Logos

Do you prefer a "grown-up" or child friendly design?

Do colours and pictures tend to keep your attention?

...or do you find them distracting?

Do you get bored when looking at black and white pages of questions?

Would pictures or colours make you likely to carry on with the questionnaire longer than a plain one?

Considering the purpose of this questionnaire, are themes relating to childhood relevant?

6. These next three questions are about other problems your child may have had.

Over the last three months:

1

a. My child has had noisy breathing that does not seem to come from the chest :

b. My child has had fast breathing:

c. My child has had noisy breathing that appears to come from the throat or back of the throat:

Something colourful that brightens the page without taking over?



## Liverpool Respiratory Symptom Questionnaire

6. These next three questions are about other problems your child may have had.

2

Over the last three months:

a. My child has had noisy breathing that does not seem to come from the chest :

b. My child has had fast breathing:

c. My child has had noisy breathing that appears to come from the throat or back of the throat:

A subtle theme that brings everything together?



UNIVERSITY OF LIVERPOOL

Liverpool Women's NHS Foundation Trust  
Dedicated to you

## The LRSQ

6. These next three questions are about other problems your child may have had.  
Over the last three months:

a. My child has had noisy breathing that does not seem to come from the chest :

b. My child has had fast breathing:

c. My child has had noisy breathing that appears to come from the throat or back of the throat:

Lots of bright colours?

## Font size

How important is the size of the text?

Do you find larger text overwhelming or easier to read?

## The LRSQ

6. The next three questions are about other problems that your child may have had.

Over the **LAST THREE MONTHS:**

1

a. My child has had noisy breathing that does not seem to come from the chest

Please select

b. My child has had fast breathing

Please select

c. My child has had noisy breathing that seems to come from the throat or the back of the throat.

Please select

## The LRSQ

6. The next three questions are about other problems that your child may have had.

Over the **LAST THREE MONTHS:**

2

a. My child has had noisy breathing that does not seem to come from the chest

Please select

b. My child has had fast breathing

Please select

c. My child has had noisy breathing that seems to come from the throat or the back of the throat.

Please select

**Figure 8.7: Questions asked during semi-structured interview**

**Questions used during semi-structured interview (Pickles and Griffith)**

**Before questionnaire completion**

1. First impression of questionnaire (positive or negative) Rating of appearance (scale 1-10)
2. Readability of the text
3. During Questionnaire Completion
4. Are the instructions clear
5. Understanding of information, questions and terms
6. Flow of questions – is it logical
7. Any vague or ambiguous questions
8. Is it repetitive
9. Any particular like or dislikes in terms of content or appearance

**After questionnaire completion on first survey software**

1. Was the length of the questionnaire acceptable
2. Overall rating of appearance of questionnaire (scale 1-10)

**After completion of questionnaire on both survey software**

1. Overall preference
2. Question preference – Matrix tables or drop-down boxes Any additional comment

**After reviewing recruitment material (time permitting)**

1. General impression of recruitment material
2. Is the information clear and readable
3. QR codes: do they recognise them, know how to use them, and do they use them
4. Any other factors that would affect their likelihood to complete the questionnaire

## Appendix 5: LRBCS Initial Questionnaire

On the subsequent page is the Initial LRBCS Questionnaire that has been deployed to study participants since the end of May 2013 (Figure 8.7). This is the initial questionnaire deployed to mothers 4 months after the birth of their new baby. The repeated questionnaire has been adapted so that it is relevant for the child in question.



**Figure 8.8: LRBCS Initial Questionnaire (PDF Postal Version)**



Welcome, and thank you for your interest in...  
**Liverpool Baby Breathing Study**

**Questionnaire 1**

The following questionnaire asks questions about your baby and what has been happening to him or her over the last three months. It should take **no longer than 10 minutes to complete**. All future questionnaires should take no more than 5 minutes to complete.

This study aims to find out more about the respiratory symptoms, such as wheezing, coughs and colds, that your child experiences, and how they affect you and your family.

Our study will help us understand what makes these symptoms more or less likely to occur and how they change over time.

It is important that every question is answered, even if your child has been perfectly well, with no problems at all.

Thank you.

---

**Further Information**

**01.05.2013**

**Why have I been chosen?**

We are asking all parents of children born at the Liverpool Women's Hospital who were living within the L1-38 post codes when their child was born to take part. We are particularly interested in the children of Liverpool as there are high levels of respiratory diseases such as asthma and bronchiolitis.

**Do I have to take part?**

No - it is up to you whether you decide to take part or not. You are free to withdraw at any time, without giving a reason. You and your child's future clinical care will not be affected if you do not wish to take part.

**What will it involve (before/during/after?)**

- We ask you to complete a questionnaire about your child. We will email you a link to the questionnaire just twice a year for five years.
- This questionnaire should take no longer than 10 minutes to complete.
- We will be asking you a few questions about your family circumstances, and your child's respiratory symptoms.
- You can choose to receive updates on how the study is running by email. At the end of the study, we will send you a summary of the results for the whole study.

**Are there disadvantages of taking part?**

We are not aware of any disadvantages to you or your child. All information will be treated with the strictest confidence.

**Are there any advantages for taking part?**

Being involved in the study will not benefit your child directly. We hope to help other children in the future by identifying what helps or worsens respiratory symptoms.

*If you have any further questions, please contact the research team directly:*

Email: [BabyStudy@liverpool.ac.uk](mailto:BabyStudy@liverpool.ac.uk)  
Telephone: (0151) 282 4532

Please let us know if you would not like to receive any further contact from us, or if you want to go green and start receiving your questionnaires by email!



## About Your Pregnancy, Birth and New Baby

You will only need to give us these details once

1. What is your new baby's first name?

2. What is your new baby's last name?

3. Is your new baby:

☐ Male ☐ Female

4. What is your new baby's date of birth?

5. What best describes your new baby's ethnic group or background?

- ☐ I would prefer not to say  
☐ White - British  
☐ White - Any other white background  
☐ Mixed or multiple ethnic groups  
☐ African, Caribbean or any other black ethnic group  
☐ Asian - Indian, Pakistani or Bangladeshi or any other ethnic group  
☐ Eastern Asian- Chinese or any other ethnic group  
☐ Other - Please Specify

6. How many weeks pregnant were you when you gave birth? e.g. if you gave birth at 36 weeks 5 days , please write "36"

7. How much did your baby weigh at birth?

8. Did **you** smoke at *any time* during your pregnancy?

☐ Yes ☐ No

9. Did **any member** of your household smoke, *anywhere* or at *any time during your pregnancy*?

A household member means someone who sleeps or regularly takes meals at your house.

☐ Yes ☐ No

Where did these people smoke?

*Tick all that apply*

- ☐ Inside the home  
☐ Outside the home  
☐ Inside the car  
☐ Inside at another location eg. work/social  
☐ Other

10. Did you breast feed your new baby at any time? *This includes expressed breast milk or bottle feeding at the same time*

☐ Yes ☐ No

If yes, how long did you breast feed for?

☐ Less than 1 month ☐ 1-3 months ☐ I am still breast feeding



## About You and Your Household

Your information will be stored securely and will not be shared

11. Which of these qualifications do you have?

- ☐ No qualifications  
☐ Completed secondary school  
☐ GCSE/O-Level  
☐ Vocational Training/ Apprenticeship  
☐ Diploma eg. BTEC, GNVQ  
☐ A Levels/Scottish Highers  
☐ Undergraduate Degree  
☐ Postgraduate Degree  
☐ Other (please specify)

12. Have you, your baby's father, or any of your baby's brothers or sisters ever been told by a doctor that they, or you, have of asthma, hay fever or eczema?

- ☐ Yes   ☐ No

If you answered yes to the question above, who has Asthma, Hay Fever or Eczema?

	Asthma	Hay Fever	Eczema
Me (My baby's mother)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
My baby's father	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
My eldest child	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
My second eldest child	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
My third eldest child	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
My fourth eldest child	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

13. Does **any member** in your household smoke, anywhere?

*A household member means someone who sleeps or regularly takes meals at your house. Please tick yes, even if they smoke outside*

- ☐ Yes   ☐ No

If yes, where do these people smoke?

*Tick all that apply*

- ☐ Inside the home  
☐ Outside the home  
☐ Inside the car  
☐ Inside at another location eg. work/social  
☐ Other

14. Does your baby attend nursery/crèche?

- ☐ Yes   ☐ No



## About Your New Baby

15. Do you have any other children who live with you?

☐ Yes ☐ No

If yes, how many other children live with you?

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 or more

16. Does your baby share a bedroom with yourself or anybody else?

☐ Yes ☐ No

If yes, who does your baby share a bedroom with?

*Please tick all that apply*

☐ Parent or parents ☐ One other child ☐ Two or more children  
☐ Other

17. Has your new baby ever seen your GP because of his/her chest?

☐ Yes ☐ No

If yes, how many times has your baby seen your GP because of his/her chest?

☐ Once ☐ Twice ☐ Three times ☐ Four times ☐ Five times  
☐ More than 5 times

18. Has your new baby ever been to hospital because of his/her chest?

☐ Yes ☐ No

If yes, how many times has your baby been to hospital because of his/her chest?

☐ Once ☐ Twice ☐ Three times ☐ Four times ☐ Five times  
☐ More than 5 times

19. Does your new baby have any long term health conditions?

☐ Yes ☐ No

What kind of long term health condition does your new baby have?

☐ Long term chest (respiratory) disease?  
☐ Long term heart disease?  
☐ Long term kidney disease?  
☐ Long term neurological disease?  
☐ Diabetes?  
☐ Other

Please tell us more about the long term health condition(s) your new baby has:



## Your New Baby's Health

### During the DAY(when awake) in the last three months::

20. My new baby has been wheezing (*whistling noise coming from the chest*)

- ☐ Not at all
 ☐ A few days
 ☐ Some days
 ☐ Most days
 ☐ Every day

21. My new baby has had a cough

- ☐ Not at all
 ☐ A few days
 ☐ Some days
 ☐ Most days
 ☐ Every day

22. My new baby has had a rattly chest (*noise that you can hear and feel as a vibration, when placing your hands over your baby's chest*)

- ☐ Not at all
 ☐ A few days
 ☐ Some days
 ☐ Most days
 ☐ Every day

23. My new baby has been short of breath

- ☐ Not at all
 ☐ A few days
 ☐ Some days
 ☐ Most days
 ☐ Every day

---

### During the NIGHT (when asleep) in the last three months:

24. My new baby has been wheezing (*whistling noise coming from the chest*)

- ☐ Not at all
 ☐ A few nights
 ☐ Some nights
 ☐ Most nights
 ☐ Every night

25. My new baby has had a cough

- ☐ Not at all
 ☐ A few nights
 ☐ Some nights
 ☐ Most nights
 ☐ Every night

26. My new baby has had a rattly chest (*noise that you can hear and feel as a vibration when placing your hands over your child's chest*)

- ☐ Not at all
 ☐ A few nights
 ☐ Some nights
 ☐ Most nights
 ☐ Every night

27. My new baby has been short of breath

- ☐ Not at all
 ☐ A few nights
 ☐ Most nights
 ☐ Some nights
 ☐ Every night

28. My new baby has snored:

- ☐ Not at all
 ☐ A few nights
 ☐ Most nights
 ☐ Some nights
 ☐ Every night





## Your New Baby's Health

29. How many colds (*runny nose, and high temperature*) has your new baby had in the last three months?

- ☐ 0
 ☐ 1
 ☐ 2
 ☐ 3
 ☐ 4
 ☐ More than 4

### When my new baby has HAD A COLD in the last three months:

30. My new baby has been wheezing (*whistling noise coming from the chest*)

- ☐ Not at all with colds
 ☐ A few days
 ☐ Some days
 ☐ Most days
 ☐ Every day

31. My new baby has had a cough

- ☐ Not at all with colds
 ☐ A few days
 ☐ Some days
 ☐ Most days
 ☐ Every day

32. My new baby has had a rattly chest (*noise that you can hear and feel as a vibration when placing your hands over your child's chest*)

- ☐ Not at all with colds
 ☐ A few days
 ☐ Some days
 ☐ Most days
 ☐ Every day

33. My new baby has been short of breath

- ☐ Not at all with colds
 ☐ A few days
 ☐ Some days
 ☐ Most days
 ☐ Every day

### When my new baby has NOT HAD A COLD in the last three months:

34. My new baby has been wheezing (*whistling noise coming from the chest*)

- ☐ Not at all
 ☐ A few days
 ☐ Some days
 ☐ Most days
 ☐ Every day

35. My new baby has had a cough

- ☐ Not at all
 ☐ A few days
 ☐ Some days
 ☐ Most days
 ☐ Every day

36. My new baby has had a rattly chest (*noise that you can hear and feel as a vibration when placing your hands over your child's chest*)

- ☐ Not at all
 ☐ A few days
 ☐ Some days
 ☐ Most days
 ☐ Every day

37. My new baby has been short of breath

- ☐ Not at all
 ☐ A few days
 ☐ Some days
 ☐ Most days
 ☐ Every day



## Your New Baby's Health

**When my new baby has been more active (e.g. crawling, walking or when excited) in the last three months:**

38. My new baby has been wheezing (*whistling noise coming from the chest*)

- ☐ Not at all    ☐ A few days    ☐ Some days    ☐ Most days    ☐ Every day

39. My new baby has had a cough

- ☐ Not at all    ☐ A few days    ☐ Some days    ☐ Most days    ☐ Every day

40. My new baby has had a rattly chest (*noise that you can hear and feel as a vibration when placing your hands over your child's chest*)

- ☐ Not at all    ☐ A few days    ☐ Some days    ☐ Most days    ☐ Every day

41. My new baby has been short of breath

- ☐ Not at all    ☐ A few days    ☐ Some days    ☐ Most days    ☐ Every day

---

**Other problems my new baby may have had in the last three months:**

42. My new baby has had noisy breathing that does not seem to come from the chest:

- ☐ Not at all    ☐ A few days    ☐ Some days    ☐ Most days    ☐ Every day

43. My new baby has had fast breathing:

- ☐ Not at all    ☐ A few days    ☐ Some days    ☐ Most days    ☐ Every day

44. My new baby has had noisy breathing that appears to come from the throat or back of the throat:

- ☐ Not at all    ☐ A few days    ☐ Some days    ☐ Most days    ☐ Every day



## Your New Baby's Health

### How my new baby's chest symptoms actually affected him or her over the last three months:

45. My new baby's chest symptoms have affected his or her feeding or eating

- ☐ Not at all    ☐ A few days    ☐ Some days    ☐ Most days    ☐ Every day

46. My new baby's chest symptoms have woken up my new baby:

- ☐ Not at all    ☐ A few nights    ☐ Some nights    ☐ Most nights    ☐ Every night

47. My new baby's chest symptoms have reduced my new baby's activity:

- ☐ Not at all    ☐ A few days    ☐ Some days    ☐ Most days    ☐ Every day

48. My new baby's chest symptoms have made my new baby unusually tired:

- ☐ Not at all    ☐ A few days    ☐ Some days    ☐ Most days    ☐ Every day

---

### How my new baby's chest symptoms have affected *me and my family* in the last three months:

49. My new baby's chest symptoms have limited MY activities:

- ☐ Not at all    ☐ A few days    ☐ Some days    ☐ Most days    ☐ Every day

50. My new baby's symptoms have resulted in adjustments being made to our family life:

- ☐ Not at all    ☐ A few days    ☐ Some days    ☐ Most days    ☐ Every day

51. My new baby's chest symptoms have disturbed our sleep:

- ☐ Not at all    ☐ A few nights    ☐ Some nights    ☐ Most nights    ☐ Every night

52. I have been worried about my new baby's chest symptoms:

- ☐ Not at all    ☐ A few days    ☐ Some days    ☐ Most days    ☐ Every day





## Your Details

Your data will be stored securely and will not be shared

**You will only need to give us these details once!**

53. What is **your** first name?

54. What is **your** last name?

55. What is your new baby's **father's** first name? *(optional)*

56. What is your new baby's **father's** last name? *(optional)*

57. What is your full address

58. What is your **postcode**?

59. What is your **main** telephone number?

60. What is your **main** e-mail address?

☐ I would like to receive my future questionnaires online

☐ I want to sign up to the Liverpool Baby Study newsletter to receive updates from the study



## The Liverpool Respiratory Birth Cohort Study

**Thank You For Your Participation!**

**All the information you give us is invaluable to the research team and future children in Liverpool, even if your baby hasn't had any symptoms at all!** We will be in touch with you again in around 6 months time.

If you have any questions or would like to discuss the study with the research team, please don't hesitate to contact the research team at [babystudy@liverpool.ac.uk](mailto:babystudy@liverpool.ac.uk) or call us on 0151 282 4532

MG Semple  
Institute of Child Health,  
University of Liverpool,  
Alder Hey Children's Hospital NHS FT,  
Eaton Road,  
Liverpool,  
Merseyside  
L12 2AP



## Figure 8 10: Initial Application for Funding Document

### Request for support

The study will be conducted over a minimum of 6 years. Recruitment will take place during the first year of the study, and children will be followed up biannually until the last child to be recruited has reached his or her fifth birthday. Prior to the research team commencing with recruitment, financial support is required for the survey software, mailing system, and also the printing of postcards.

### Software

*Item Requested:* Adobe Forms Central subscription@ £105.39/year [for 6 years] = £632.34, paid yearly

*Justification of this particular software:* The majority of participants of a feasibility study preferred this software. It also allows multiple contributors to edit the appearance of the questionnaire in real-time. Other important features include question skip logic, which allows only relevant questions to be asked to participants, thus reducing the overall time taken to complete the study and allows a better flow through the survey. Furthermore, Adobe forms lets use “help” buttons, headers and footers to give extra information to guide participants through the questionnaire without cluttering the page. Progression through the survey is clearly demonstrated with a percentage progress bar. It offers the research team the flexibility to add unlimited logos and images, which will aid parents to quickly identify the study, in addition to giving the questionnaire a more professional appearance.

These features combined give Adobe a superior survey experience for participants, which we hope will encourage parents to continue to return to the questionnaire for the whole duration of the study.

## Email

*Item Requested:* 35,000 MailChimp® credits [=35,000 emails] a year.

*Justification:* MailChimp® offers either a monthly subscription or a “pay-as-you go” option. Due to the frequency and volume of messages that will be sent by the LRBCS, purchasing credits is the most economical option. This amount is sufficient for the maximum recruitment of the 8,500 infants born at Liverpool Women’s every year to be sent four emails per year (see email schedule). In the event of more emails being required, these can be purchased at a later date. The research team will re-appraise this number at the end of recruitment, when the total maximum number of emails can be calculated. An effective, professional and reliable email service is core to the success of the LRBCS, and it is felt that utilizing MailChimp® is the only way the research team can be ascertain that this will be the case.

## Postcards

*Item Requested:* 8,500 information and sign-up postcards to be distributed to all mothers of newborn infants born at Liverpool Women’s Hospital. Companies offer batches of either 7,500 or 10,000, therefore 10,000 postcards will be needed to ensure there are sufficient quantities to meet the maximum recruitment strategy. The estimated cost of this after researching the cheapest options is using:-

Print24 who will provide 10,000 postcards A5, double-sided colour 250gsm, matt finish at £223.93.

It is cheaper to order postcards in bulk rather to buy batches of smaller quantities.

*Justification:* These are central to the research team’s recruitment strategy. The NRES committee have approved the design and content of the postcard. The postcards must be A5 size in order to ensure they are legible. They must be in colour to encourage interest as it will significantly improve the aesthetic appeal, as well as ensuring that continuity between the stationary and the online forms. Postcards will need either a matt or silk finish to ensure potential participants can write on the cards using a pen.

### Start-Up (Cost year 1)

The estimated cost of start-up is £486.05, which includes the initial year's subscription to Adobe, the 10,000 postcards needed and 25,000 email credits.

Resource	Amount/Duration	Cost	Total
<b>Adobe Forms Central Subscription</b>	1 year	£105.39/year	£105.39
<b>MailChimp® Email Credits</b>	25,000 email credits	£156.73	£156.73
<b>Postcards (A5)</b>	10,000	£223.93	£223.93
		<b>Total</b>	<b>£486.05</b>

### Running Cost (Years 2 through 6)

The running cost calculated from years 2 through 6, which includes five further years subscription to Adobe, recruitment postcards and sufficient emailing credits.

Resource	Amount/Duration	Cost	Total
<b>Adobe Forms Central Subscription</b>	5 years	£105.39/year	£526.95
<b>MailChimp® Email Credits</b>	200,000 (bulk order)	NA	£626.92
<b>Postcards (A5)</b>	10,000 x 5 years	£223.93	£1119.65
		<b>Year 2-6 total</b>	<b>£2273.52</b>

**Total Cost (Recruitment + Follow up)**

<b>Resource</b>	<b>Amount/Duration</b>	<b>Cost</b>	<b>Total</b>
<b>Adobe Forms Central Subscription</b>	6 years	£105.39/year	£626.34
<b>MailChimp® Email Credits</b>	225,000	NA	£783.65
<b>Postcards (A5)</b>	10,000 x 6 years	£223.93	£1343.58
<b>Year 2-6 total</b>			<b>£2759.57</b>

For the initial recruitment and follow-up of up to 8,500 infants born at Liverpool Women's Hospital annually from January 2013, the estimated total cost will be £486.05 + £2273.52 = **£2759.57**

## Appendix 6: Statistical Results

**Figure 8.11 – Calculation Matrix used for Chi squared calculation of IMD quintiles and expressed interest, consented and births at the LWH.**

	Gp 1	Gp 2	Gp 3	Gp 4	Gp 5	Gp 6	Gp 7	Gp 8	Gp 9	Gp 10
Cond. 1:	0	0	0							0
Cond. 2:	2	2	5							9
Cond. 3:	24	12	48							84
Cond. 4:	60	10	87							157
Cond. 5:	293	56	413							762
Cond. 6:										0
Cond. 7:										0
Cond. 8:										0
Cond. 9:										0
Cond. 10:										0
	379	80	553	0	0	0	0	0	0	1012

Output:

Calculate    Reset all

Chi-square: 10.122

degrees of freedom: 6

p-value: 0.11960746

Yates' chi-square: 7.024

Yates' p-value: 0.3186334

Status: At least one expected frequency is less than 1 !!

**Table 8.5: Figures used for Chi Squared Calculation**

IMD Quintiles	Expressed Interest	Consented	LWH Births	Total
1 <sup>st</sup>	0	0	0	0
2 <sup>nd</sup>	2	2	5	9
3 <sup>rd</sup>	24	12	48	84
4 <sup>th</sup>	60	10	87	157
5th	293	56	413	762
Total	379	80	553	1012
Chi squared				10.122
p value				0.1196

## Appendix 7 – Mailing Schedule

**Figure 8.12: Email Schedule from sign up to end of study (Courtesy of B. Griffith)**

1. **Immediately after sign up:** Welcome/ Thank you for your interest email – sent immediately after they sign up online, or as soon as we receive their details – will tell them we will be in touch when baby is 4 months old.
2. **4 Months:** Email link to form 1 that contains: consent, further information, demographics, exposures, LRSQ. Also allow them to subscribe to updates from study.
3. **10 Months:** Email link to form 2 that contains: exposures + LRSQ – check no changes to details at end. Also allow them to subscribe to updates from study.
4. **12 Months:** *Happy 1st Birthday email* – congratulate. Check that details have not changed, tell them we will be in touch with another questionnaire in 4 months time. Also allow them to subscribe to updates from study.
5. **16 Months:** Email link to form 3 that contains exposures + LRSQ – check no changes to details at end. Also allow them to subscribe to updates from study.
6. **22 Months:** Email link to form 4 that contains exposures + LRSQ – check no changes to details at end. Also allow them to subscribe to updates from study.
7. **24 Months:** *Happy 2nd Birthday email* – congratulate. Check that details have not changed, tell them we will be in touch with another questionnaire in 4 months time. Also allow them to subscribe to updates from study.
8. **28 Months:** Email link to form 5 that contains exposures + LRSQ – check no changes to details at end. Also allow them to subscribe to updates from study.
9. **34 Months:** Email link to form 6 that contains exposures + LRSQ – check no changes to details at end. Also allow them to subscribe to updates from study.
10. **36 Months:** *Happy 3rd Birthday email* – congratulate. Check that details have not changed, tell them we will be in touch with another questionnaire in 4 months time. Also allow them to subscribe to updates from study.
11. **40 Months:** Email link to form 7 that contains exposures + LRSQ – check no changes to details at end. Also allow them to subscribe to updates from study.
12. **46 Months:** Email link to form 8 that contains exposures + LRSQ – check no changes to details at end. Also allow them to subscribe to updates from study.
13. **48 Months:** *Happy 4th Birthday email* – congratulate. Check that details have not changed, tell them we will be in touch with another questionnaire in 4 months time. Also allow them to subscribe to updates from study.
14. **52 Months:** Email link to form 9 that contains exposures + LRSQ – check no changes to details at end. Also allow them to subscribe to updates from study.
15. **58 Months:** Email link to form 10 that contains exposures + LRSQ – check no changes to details at end. Also allow them to subscribe to updates from study.
16. **60 Months:** *Happy 5th birthday email* – congratulate. Thank them for participation and clarify that there will be no more questionnaires. Ask if they would still like to receive updates for the study.

Each email will be generated to contain: Parent's name, Child's name, Unique study ID of the child. Technology also allows us to add the address and telephone number that we currently hold for them (in case it needs to be changed).